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USPT,JPAB,EPAB,DWPI,TDBD	(Jak? kinase) adj cDNA	0	L6
USPT,JPAB,EPAB,DWPI,TDBD	L4 and ((JAK? kinase) adj DNA)	0	L5
USPT,JPAB,EPAB,DWPI,TDBD	L3 and cytokine	35	L4
USPT,JPAB,EPAB,DWPI,TDBD	L2 and (tyrosine phosphorylation)	39	L3
USPT,JPAB,EPAB,DWPI,TDBD	L1 and DNA	47	L2
USPT,JPAB,EPAB,DWPI,TDBD	JAK kinase	53	L1

We have cloned and sequenced a *cDNA* (*JAK3*) encoding a novel member of the JAK family of protein tyrosine kinases. *JAK3* was identified by RT-PCR of rat mesangial cells using degenerate oligonucleotide primers, and a full-length clone was isolated from a rat spleen *cDNA* library. The primary structure of *JAK3* showed *cDNA* with an open reading frame of 1,100 amino acids which comprises the PTK catalytic domain and a second kinase-related domain characteristic for *JAK* *kinase*. *JAK3* was phylogenetically shown to be most closely related to JAK2 among the previously known JAK family members, JAK1, JAK2 and Tyk2. Southern analysis revealed that *JAK3* is a single copy *gene* and well conserved in the vertebral genome. Northern analysis indicated that the 4.0 kb rnRNA was transcribed in a variety of tissues including spleen...

16/3,K/17 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10316531 BIOSIS NO.: 199698771449
Murine *JAK3* is preferentially expressed in hematopoietic tissues and lymphocyte precursor cells.
AUTHOR: Gurniak Christine B; Berg Leslie J(a)
AUTHOR ADDRESS: (a)Dep. Mol., Cellular Biol., Harvard Univ., 16 Divinity Ave., Cambridge, MA 02138**USA
JOURNAL: Blood 87 (8):p3151-3160 1996
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Murine *JAK3* is preferentially expressed in hematopoietic tissues and lymphocyte precursor cells.

...ABSTRACT: of cytokine receptor signal transduction in T-cell development, we have investigated the expression pattern and biochemical characteristics of the murine Janus family tyrosine kinase, *JAK3*. Previous studies have shown that *JAK3* is expressed in lymphoid and myeloid tumor cell lines and in a small number of lymphoid tissues. To further characterize *JAK3* expression, we used a quantitative polymerase chain reaction approach to compare *JAK3* mRNA levels at multiple stages of T-cell differentiation and in a broad range of mouse tissues. These studies, in conjunction with analyses of *JAK3* protein expression, show that the highest levels of *JAK3* are in adult, 2-week-old, and fetal thymus, followed by somewhat lower levels in bone marrow, spleen, fetal liver, and adult CD4-CD8- thymocytes. We also show that different forms of *JAK3* MRNA arise by alternative splicing, Finally, our biochemical studies show that the *JAK3* *kinase* domain, but not the pseudo-kinase domain, has tyrosine kinase activity and, furthermore, that *JAK3* *kinase* activity is abolished by an amino acid substitution of the conserved lysine in the kinase domain (K851R). These studies show that *JAK3* expression is profoundly skewed to hematopoietic and lymphoid precursor cells, strongly suggesting a role for *JAK3* in hematopoiesis and T- and B-cell development.
MISCELLANEOUS TERMS: ...*GENE* EXPRESSION

16/3,K/18 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10055344 BIOSIS NO.: 199598510262
JAK protein tyrosine kinase mediates interleukin-7-induced activation of phosphatidylinositol-3' kinase.
AUTHOR: Sharfe Nigel; Dadi Harjit K; Roifman Chaim M(a)
AUTHOR ADDRESS: (a)Dep. Immunol. Allergy, Hosp. Sick Children, 555

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***The Mirror Group Publications (United Kingdom) (File 757)

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***TFSD Ownership Database (File 540)
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       18feb01 12:56:35 User259876 Session D188.1
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          $0.40    0.113 DialUnits File1
     $0.40  Estimated cost File1
     $0.01  TYMNET
     $0.41  Estimated cost this search
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?s (JAK? (w) kinase?)
            19983  JAK?
           465391  KINASE?
       S1     759  (JAK? (W) KINASE?)
?s s1 and (DNA or vector?)
             759  S1
         1570723  DNA
          221245  VECTOR?
       S2     261  S1 AND (DNA OR VECTOR?)
?s s2 and (tyrosine (w) phosphorylation)
             261  S2
          210595  TYROSINE
          224543  PHOSPHORYLATION
           29972  TYROSINE(W)PHOSPHORYLATION
       S3     112  S2 AND (TYROSINE (W) PHOSPHORYLATION)
?s s3 and (cytokine?)
             112  S3
          229502  CYTOKINE?
       S4      65  S3 AND (CYTOKINE?)
?rd
...examined 50 records  (50)
...completed examining records
       S5      34  RD (unique items)
?t s5/3,k/1-10

 5/3,K/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10570639   20440187
 Regulation of STAT1 nuclear export by Jak1.
  Mowen K; David M
  Department of Biology, University of California at San Diego, La Jolla,
California 92093, USA.
  Molecular and cellular biology (UNITED STATES)  Oct 2000,  20 (19)
p7273-81, ISSN 0270-7306  Journal Code: NGY
  Contract/Grant No.: CA80105, CA, NCI
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE

  Signal transducer and activator of transcription 1 (STAT1) mediates gene
expression in response to *cytokines* and growth factors. Activation of
STAT1 is achieved through its *tyrosine* *phosphorylation*, a process that
involves Jak tyrosine kinases. Here we show that STAT1, although
phosphorylated on Y701, is unable to localize in the nucleus in the absence
```

of Jak1 or *Jak1* *kinase* activity. In contrast, the nuclear accumulation of STAT1 in Tyk2-deficient cells remains intact. Nuclear presence of tyrosine-phosphorylated STAT1 could be restored in Jak1...
Descriptors: Cell Nucleus--Metabolism--ME; **DNA*-Binding Proteins --Metabolism--ME; *Nuclear Proteins--Metabolism--ME; *Protein-Tyrosine Kinase--Physiology--PH; *Signal Transduction--Physiology--PH; *Trans-Activators--Metabolism--ME; Amino Acid Sequence; Biological Transport --Drug Effects--DE; Cells, Cultured--Metabolism--ME; Dimerization; *DNA* --Metabolism--ME; *DNA*-Binding Proteins--Chemistry--CH; Fatty Acids, Unsaturated--Pharmacology--PD; Hela Cells--Metabolism--ME; Interferons --Pharmacology--PD; Models, Molecular; Neoplasm Proteins--Metabolism--ME; Phosphorylation; Protein Binding...
Chemical Name: Janus kinase 1; (Protein-Tyrosine Kinase; (gamma-activated factor, 91-kD; (CREB-binding protein; (*DNA*-Binding Proteins; (Fatty Acids, Unsaturated; (Neoplasm Proteins; (Nuclear Proteins; (Proteins; (Recombinant Fusion Proteins; (Signal Peptides; (Trans-Activators; (tyk2 protein; (leptomycin B; (*DNA*; (Interferons

5/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10435328 20309845
IL-3 signaling and the role of Src kinases, JAKs and STATs: a covert liaison unveiled.
Reddy EP; Korapati A; Chaturvedi P; Rane S
Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, 3307 N Broad Street, Philadelphia, Pennsylvania, PA 19140, USA.
Oncogene (ENGLAND) May 15 2000, 19 (21) p2532-47, ISSN 0950-9232
Journal Code: ONC
Contract/Grant No.: CA98239, CA, NCI; ES09225, ES, NIEHS
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC

Hematopoiesis is the cumulative result of intricately regulated signal transduction cascades that are mediated by *cytokines* and their cognate receptors. Proper culmination of these diverse signaling pathways forms the basis for an orderly generation of different cell types and aberrations in these pathways is an underlying cause for diseases such as cancer. Over the past several years, downstream events initiated upon *cytokine*/growth factor stimulation have been a major focus of biomedical research. As a result, several key concepts have emerged allowing a better understanding of the complex signaling processes. A group of novel transcription factors, termed signal transducers and activators of transcription (STATs) appear to orchestrate the downstream events propagated by *cytokine*/growth factor interactions with their cognate receptors. Until recently, the JAK proteins were considered to be the tyrosine kinases, which dictated the levels of phosphorylation...

... evidence has accumulated which indicates that at least some of the STAT protein activation may be mediated by members of the Src gene family following *cytokine* /growth factor stimulation. Studies have demonstrated that the Src-family of tyrosine kinases can phosphorylate and activate certain STAT proteins, in lieu of *JAK* *kinases*. In such a scenario, *JAK* *kinases* may be more crucial to phosphorylation of the *cytokine* /growth factor receptors and in the process create docking sites on the receptors for binding of SH2-containing proteins such as STATs, Src-kinases and other signaling intermediates. *Tyrosine* *phosphorylation* and activation of STAT proteins can be achieved either by JAKs or Src-kinases depending on the nature of STAT that is being activated. This forms the basis for the JAK-Src-STAT model proposed in this review. The concerted action of *JAK* *kinases* , members of the Src-kinase family and STAT proteins, leads to cell proliferation and cell survival, the end-point of the *cytokine*/growth factor stimulus. Oncogene (2000).

Descriptors: src-Family Kinases--Metabolism--ME; **DNA*-Binding Proteins --Metabolism--ME; *Interleukin-3--Metabolism--ME; *Protein-Tyrosine Kinase --Metabolism--ME; *Signal Transduction; *Trans-Activators--Metabolism--ME; Apoptosis; *Cytokines*--Metabolism--ME; Receptors, Interleukin-3 --Metabolism--ME; Trans-Activation (Genetics); 1-Phosphatidylinositol 3-Kinase--Metabolism--ME

Chemical Name: Janus kinase 1; (Protein-Tyrosine Kinase; (1-Phosphatidylinositol 3-Kinase; (src-Family Kinases; (gamma-activated factor, 91-kD; (*Cytokines*; (*DNA-Binding Proteins*; (Interleukin-3; (Receptors, Interleukin-3; (Trans-Activators

5/3,K/3 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10434939 20245593

The Jak-STAT pathway.

Imada K; Leonard WJ

Laboratory of Molecular Immunology, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD 20892-1674, USA.

Molecular immunology (ENGLAND) Jan-Feb 2000, 37 (1-2) p1-11, ISSN 0161-5890 Journal Code: NG1

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

A variety of important cellular functions are regulated by *cytokines*. The Jak-STAT pathway is one of the important signaling pathways downstream of *cytokine* receptors. Following binding of a ligand to its cognate receptor, receptor-associated Jaks are activated. STAT proteins are then in turn activated by *tyrosine* *phosphorylation* by *Jak* *kinases*, allowing their dimerization and subsequent translocation into the nucleus, where they modulate expression of target genes. Indispensable functions of Jaks and STATs in *cytokine* signaling in vivo have been revealed through knockout mouse studies. Moreover, the recent discovery of the CIS/SOCS/JAB/SSI family of inhibitors has contributed...

Descriptors: *DNA*-Binding Proteins--Physiology--PH; *Protein-Tyrosine Kinase--Physiology--PH; *Trans-Activators--Physiology--PH

Chemical Name: Janus kinase 1; (Janus kinase 2; (Janus kinase 3; (Protein-Tyrosine Kinase; (gamma-activated factor, 91-kD; (mammary gland-specific nuclear factor; (transcription factor Stat4; (*DNA*-Binding Proteins; (Interleukin-2; (Stat3 protein; (Trans-Activators; (Stat6 protein

5/3,K/4 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10233854 20054432

SOCS/CIS protein inhibition of growth hormone-stimulated STAT5 signaling by multiple mechanisms.

Ram PA; Waxman DJ

Department of Biology, Division of Cell Biology, Boston University, Boston, Massachusetts 02215, USA.

Journal of biological chemistry (UNITED STATES) Dec 10 1999, 274 (50) p35553-61, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: DK33765, DK, NIDDK

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The inhibition of growth hormone (GH) signaling by five members of the GH-inducible suppressor of *cytokine* signaling (SOCS/CIS) family was investigated in transfected COS cells. Complete inhibition of GH activation of the signal transducer STAT5b and STAT5b-dependent transcriptional activity...

... 6) was seen with other SOCS/CIS family members. SOCS-1, SOCS-2, SOCS-3, and CIS each strongly inhibited the GH receptor (GHR)-dependent *tyrosine* *phosphorylation* of JAK2 seen at low levels of transfected JAK2; however, only SOCS-1 strongly inhibited the GHR-independent *tyrosine* *phosphorylation* of JAK2 seen at higher JAK2 levels. To probe for interactions with GHR, in vitro binding assays were carried out using glutathione S-transferase-GHR...

... GHR residues, provided the fusion protein was tyrosine-phosphorylated. By contrast, SOCS-3 binding required tyrosine-phosphorylated GHR membrane-proximal sequences, SOCS-1 binding was *tyrosine* *phosphorylation* -independent, and SOCS-6 did not bind the GHR fusion proteins at all. Mutation of GHR's membrane-proximal tyrosine residues 333 and 338 to...

... GH signaling to STAT5b by three distinct mechanisms, distinguished by their molecular targets within the GHR-JAK2 signaling complex, as exemplified by SOCS-1 (direct *JAK2* *kinase* inhibition), SOCS-3 (inhibition of JAK2 signaling via membrane-proximal GHR tyrosines 333 and 338), and CIS and SOCS-2 (inhibition via membrane-distal tyrosine...

Descriptors: Carrier Proteins--Metabolism--ME; **DNA*-Binding Proteins --Metabolism--ME; *Immediate-Early Proteins--Metabolism--ME; *Proteins --Metabolism--ME; *Receptors, Somatotropin--Physiology--PH; *Signal Transduction--Physiology--PH; *Somatotropin--Pharmacology--PD; *Trans-Activ ators...

; src Homology Domains; Cell Line; Cloning, Molecular; *DNA*-Binding Proteins--Genetics--GE; Hypophysectomy; Rats; Rats, Inbred F344; Receptors, Somatotropin--Drug Effects--DE; Recombinant Fusion Proteins--Drug Effects --DE; Recombinant Fusion Proteins--Metabolism--ME...

Chemical Name: mammary gland-specific nuclear factor; (Carrier Proteins; (CIS protein; (*DNA*-Binding Proteins; (Immediate-Early Proteins; (Proteins; (Receptors, Somatotropin; (Recombinant Fusion Proteins; (SOCS-1 protein; (SOCS-2 protein; (SOCS-3 protein; (Trans-Activators; (Somatotropin

5/3,K/5 (Item 5 from file: 155)

10063190 99382146

Tumor necrosis factor-alpha signals to the IFN-gamma receptor complex to increase Stat1alpha activation.

Han Y; Rogers N; Ransohoff RM
Department of Neurosciences, The Lerner Research Institute, Cleveland Clinic Foundation, OH 44195, USA.

Journal of interferon & cytokine research (UNITED STATES) Jul 1999, 19 (7) p731-40, ISSN 1079-9907 Journal Code: CD4
Contract/Grant No.: RO1-NS 32151, NS, NINDS; PO1-CA 62220, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We describe a novel mechanism of signaling interaction through which tumor necrosis factor-alpha (TNF-alpha) treatment augments interferon-gamma (IFN-gamma)-induced Stat1alpha *DNA*-binding complexes and transcriptional activation of a Stat-binding element. In TNF-alpha-treated cells, IFN-gamma-induced phosphorylation of *Jak2* *kinase* is increased, *Jak2* *kinase* activity is enhanced, and genetic studies indicate that TNF-alpha requires *Jak2* *kinase* activity to enhance Stat1alpha *tyrosine* *phosphorylation* . Increased Jak2 and Stat1alpha phosphorylation are observed within minutes of coexposure to TNF-alpha/IFN-gamma, suggesting a direct signaling interaction. IFN-gamma receptor chain 1 (IFNGR-1) *tyrosine* *phosphorylation* is markedly enhanced in cells treated with TNF-alpha/IFN-gamma without alteration in receptor levels. Thus, there exists a direct signaling interaction between TNF-alpha and IFN-gamma, independent of cooperating enhancer elements, that may be relevant for *cytokine* action during immune-mediated host defense and inflammatory

processes.
Descriptors: *DNA*-Binding Proteins--Metabolism--ME; *Interferon Type II --Pharmacology--PD; *Receptors, Interferon--Drug Effects--DE; *Signal Transduction--Drug Effects--DE; *Transcription Factors--Metabolism--ME; *Tumor Necrosis...
Chemical Name: Janus kinase 2; (Protein-Tyrosine Kinase; (gamma interferon activation factor; (interferon gamma receptor; (*DNA*-Binding Proteins; (Receptors, Interferon; (Transcription Factors; (Tumor Necrosis Factor; (Tyrosine; (Serine; (Interferon Type II

5/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09847344 99138801
IL-4 selectively inhibits IL-2-triggered Stat5 activation, but not proliferation, in human T cells.
Castro A; Sengupta TK; Ruiz DC; Yang E; Ivashkiv LB
Department of Medicine, Hospital for Special Surgery, Cornell University Medical College, New York, NY 10021, USA.
Journal of immunology (UNITED STATES) Feb 1 1999, 162 (3) p1261-9, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

...activates several distinct signaling pathways that are important for T cell activation, proliferation, and differentiation into both Th1 and Th2 phenotypes. IL-4, the major *cytokine* that promotes differentiation of Th2 cells, has been shown to block signaling of the Th1-promoting *cytokine* IL-12. As IL-2 synergizes with IL-12 in promoting Th1 differentiation, the effects of IL-4 on IL-2 signal transduction were investigated. IL-4 suppressed activation of *DNA* binding and *tyrosine* *phosphorylation* of the transcription factor Stat5 by IL-2, and suppressed the expression of the IL-2-inducible genes CD25, CIS, the PGE2 receptor, and *cytokine* responsive (CR) genes CR1 and CR8. Activation of Stat5 by *cytokines* that share a common gamma receptor subunit, IL-2, IL-7, and IL-15, was suppressed by preculture in IL-4. Activation of the Jak1 and *Jak3* *kinases* that are proximal to Stat5 in the IL-2-Jak-STAT signaling pathway was suppressed, and this correlated with inhibition of IL-2Rbeta subunit expression...
Descriptors: *DNA*-Binding Proteins--Metabolism--ME; *Interleukin-2 --Pharmacology--PD; *Interleukin-4--Pharmacology--PD; *T-Lymphocytes --Immunology--IM; *T-Lymphocytes--Metabolism--ME; *Trans-Activators --Metabolism--ME; Base Sequence; Cell Differentiation; Cell Division; *DNA* Primers--Genetics--GE; Lymphocyte Transformation; Protein Conformation; Receptors, Interleukin-2 Receptors, Interleukin-2--Chemistry--CH; Receptors, Interleukin-2 --Metabolism--ME; Signal Transduction; T-Lymphocytes--Cytology--CY; Th1 Cells...
Chemical Name: mammary gland-specific nuclear factor; (*DNA* Primers; (*DNA*-Binding Proteins; (Interleukin-2; (Interleukin-4; (Receptors, Interleukin-2; (Trans-Activators

5/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09583565 98375861
TGF-beta inhibits IL-12-induced activation of Jak-STAT pathway in T lymphocytes.
Bright JJ; Sriram S
Multiple Sclerosis Research Laboratory, Vanderbilt University Medical Center, Nashville, TN 37212, USA.
Journal of immunology (UNITED STATES) Aug 15 1998, 161 (4) p1772-7, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH
Document type: JOURNAL ARTICLE

IL-12 is a macrophage-derived heterodimeric *cytokine* , capable of inducing proliferation, *cytokine* production, and cytotoxic activity of NK cells and T cells, and is critical for the development of Th1 responses. TGF-beta is an immunosuppressive *cytokine* that inhibits IL-12-mediated responses in NK and T cells. To determine the mechanism of action of TGF-beta, we examined its inhibitory effect on IL-12 signal-transduction pathway in T cells. Stimulation of activated T cells with IL-12 leads to *tyrosine* *phosphorylation* and activation of Jak-2 and Tyk-2 kinases and STAT3 and STAT4 transcription factors. Treatment of activated T cells with TGF-beta blocked IL-12-induced *tyrosine* *phosphorylation* and activation of both Jak-2 and Tyk-2 kinases. Furthermore, inhibition of *Jak* *kinases* by TGF-beta was associated with a decrease in *tyrosine* *phosphorylation* of STAT3 and STAT4 proteins. Abrogation of IL-12-induced Jak-Stat pathway by TGF-beta resulted in decreased T cell proliferation and IFN-gamma...
Descriptors: *DNA*-Binding Proteins--Antagonists and Inhibitors--AI; *Interleukin-12--Pharmacology--PD; *Protein-Tyrosine Kinase --Antagonists and Inhibitors--AI; *Signal Transduction--Immunology--IM; *T-Lymphocytes --Enzymology--EN...
; Apoptosis--Drug Effects--DE; Cell Cycle--Drug Effects--DE; Cells, Cultured; *DNA*-Binding Proteins--Metabolism--ME; Enzyme Activation--Drug Effects--DE; Growth Inhibitors--Pharmacology--PD; Immunosuppressive Agents --Pharmacology--PD; Interferon Type II--Antagonists and Inhibitors--AI; Interferon...
Chemical Name: Janus kinase 2; (Protein-Tyrosine Kinase; (transcription factor Stat4; (*DNA*-Binding Proteins; (Growth Inhibitors; (Immunosuppressive Agents; (Interleukin-12; (Proteins; (Stat3 protein; (Trans-Activators; (Transforming Growth Factor beta; (tyk2 protein; (Tyrosine; (Interferon Type II

5/3,K/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09513823 98241632
Jak2-Stat5 interactions analyzed in yeast.
Barahmand-Pour F; Meinke A; Groner B; Decker T
Institute of Microbiology and Genetics, Vienna Biocenter, University of Vienna, Dr. Bohr-Gasse 9, A-1030 Vienna, Austria.
Journal of biological chemistry (UNITED STATES) May 15 1998, 273 (20) p12567-75, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Many *cytokine* receptors employ Janus protein tyrosine kinases (Jaks) and signal transducers and activators of transcription (Stats) for nuclear signaling. Here, we have established yeast strains in which an autoactivated *Jak2* *kinase* induces *tyrosine* *phosphorylation* , dimerization, nuclear translocation, and *DNA* binding of a concomitantly expressed Stat5 protein. Transcriptional activity of Stat5 on a stably integrated, Stat-dependent reporter gene required the C-terminal fusion of ...

... the C terminus led to Stat5 hyperphosphorylation. A single phosphotyrosine-SH2 domain interaction was sufficient for the dimerization of Stat5, but such dimers bound to *DNA* very inefficiently. Together, our data show that yeast cells are appropriate tools for studying Jak-Stat or Stat-Stat interactions. Our mutational analysis suggests that...

...Stat5 SH2 domain is essential for the interaction with Jak2 and that the kinase domain of Jak2 is sufficient for Jak2-Stat5 interaction. Therefore, the *Jak* *kinase* domain may be all that is needed to cause Stat phosphorylation in situations where receptor docking is dispensable.

Descriptors: *DNA*-Binding Proteins--Metabolism--ME; *Protein-Tyrosine Kinase--Metabolism--ME; *Saccharomyces cerevisiae--Metabolism--ME; *Signal Transduction; *Trans-Activators--Metabolism--ME
Chemical Name: Janus kinase 2; (Protein-Tyrosine Kinase; (mammary gland-specific nuclear factor; (*DNA*-Binding Proteins; (Trans-Activators

5/3,K/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09455783 98184885
Prolactin receptor regulates Stat5 *tyrosine* *phosphorylation* and nuclear translocation by two separate pathways.
Ali S
Department of Medicine, the Division of Hematology, and the Molecular Oncology Group, Royal Victoria Hospital, McGill University, Montreal, Quebec H3A 1A1, Canada.
Journal of biological chemistry (UNITED STATES) Mar 27 1998, 273 (13) p7709-16, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Prolactin receptor regulates Stat5 *tyrosine* *phosphorylation* and nuclear translocation by two separate pathways.
The SH2 domain containing signal transducers and activators of transcription (Stat proteins) are effector molecules downstream of *cytokine* receptors. Ligand/receptor engagement triggers Stat proteins *tyrosine* *phosphorylation* , dimerization, and translocation to the nucleus where they regulate gene transcription. Stat5, originally identified as a mammary gland growth factor, is an essential mediator of prolactin (PRL)-induced milk protein gene activation. Prolactin receptor (PRLR) is a member of the *cytokine* /growth hormone/PRL receptor superfamily. The mechanism through which PRLR modulates Stat5 *tyrosine* *phosphorylation*, nuclear translocation, and *DNA* binding was analyzed in HC11 cells, a mammary epithelial cell line, and 293-LA cells, a human kidney cell line stably overexpressing *Jak2* *kinase*. We have found that in HC11 cells, Stat5 is specifically activated by PRL treatment, demonstrating that Stat5 is a physiological substrate downstream of PRLR. Furthermore, using different forms natural forms of the PRLR as well as receptor tyrosine to phenylalanine mutant forms, we determined that *tyrosine* *phosphorylation* of Stat5 is independent of PRLR phosphotyrosines. We established, however, that the C-terminal tyrosine of the PRLR Nb2 form, Tyr382, plays an essential positive role in PRLR-dependent Stat5 nuclear translocation and subsequently *DNA* binding. All together, our data propose a new model for activation of Stat5 through the PRLR, suggesting that Stat5 *tyrosine* *phosphorylation* and nuclear translocation are two separately regulated events.
Descriptors: *DNA*-Binding Proteins--Metabolism--ME; *Receptors, Prolactin--Metabolism--ME; *Trans-Activators--Metabolism--ME; *Tyrosine --Metabolism--ME; Caseins--Genetics--GE; Cell Line; Cell Nucleus --Metabolism--ME; *DNA*-Binding Proteins--Genetics--GE; Enzyme Activation; Gene Expression Regulation; Kinetics; Mice; Phosphorylation; Prolactin --Pharmacology--PD; Promoter Regions (Genetics); Protein-Tyrosine Kinase --Metabolism--ME; Trans-Activators...
Chemical Name: Janus kinase 2; (Protein-Tyrosine Kinase; (mammary gland-specific nuclear factor; (Caseins; (*DNA*-Binding Proteins; (Receptors, Prolactin; (Trans-Activators; (Tyrosine; (Prolactin

5/3,K/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09357552 98054324
Distinct *tyrosine* *phosphorylation* sites in *JAK3* *kinase* domain

positively and negatively regulate its enzymatic activity.
Zhou YJ; Hanson EP; Chen YQ; Magnuson K; Chen M; Swann PG; Wange RL; Changelian PS; O'Shea JJ
Lymphocyte Cell Biology Section, National Institutes of Health, Bethesda, MD 20892, USA. ZHOUY@arb.niams.nih.gov
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Dec 9 1997, 94 (25) p13850-5, ISSN 0027-8424
Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Distinct *tyrosine* *phosphorylation* sites in *JAK3* *kinase* domain positively and negatively regulate its enzymatic activity.
Cytokines are critically important for the growth and development of a variety of cells. Janus kinases (JAKs) associate with *cytokine* receptors and are essential for transmitting downstream *cytokine* signals. However, the regulation of the enzymatic activity of the JAKs is not well understood. Here, we investigated the role of *tyrosine* *phosphorylation* of JAK3 in regulating its kinase activity by analyzing mutations of tyrosine residues within the putative activation loop of the kinase domain. Specifically, tyrosine residues...

...In contrast, mutant Y981F had greatly increased kinase activity, whereas the double mutant, YY980/981FF, had intermediate activity. These results indicate that Y980 positively regulates *JAK3* *kinase* activity whereas Y981 negatively regulates *JAK3* *kinase* activity. These observations in JAK3 are similar to the findings in the kinase that is closely related to the JAK family, ZAP-70; mutations of...

... be critical to fully dissect the positive and negative regulatory function of these and other tyrosine residues in the control of kinase activity and hence *cytokine* signaling.
; Base Sequence; Binding Sites--Genetics--GE; COS Cells; *DNA*-Binding Proteins--Metabolism--ME; *DNA*, Complementary--Genetics--GE; Enzyme Activation; Mutagenesis, Site-Directed; Phosphorylation; Point Mutation; Protein-Tyrosine Kinase--Genetics--GE; Trans-Activators--Metabolism--ME; Tyrosine--Chemistry--CH; Tyrosine--Genetics...
Chemical Name: Janus kinase 3; (Protein-Tyrosine Kinase; (mammary gland-specific nuclear factor; (*DNA*-Binding Proteins; (*DNA* , Complementary; (Trans-Activators; (Tyrosine
?ds

Set	Items	Description
S1	759	(JAK? (W) KINASE?)
S2	261	S1 AND (DNA OR VECTOR?)
S3	112	S2 AND (TYROSINE (W) PHOSPHORYLATION)
S4	65	S3 AND (CYTOKINE?)
S5	34	RD (unique items)

```
?s s5 not py>1996
              34  S5
         5172566  PY>1996
      S6      14  S5 NOT PY>1996
?t s6/3,k/all
```

6/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09045450 96325064
An epidermal growth factor receptor/Jak2 tyrosine kinase domain chimera induces *tyrosine* *phosphorylation* of Stat5 and transduces a growth signal in hematopoietic cells.
Nakamura N; Chin H; Miyasaka N; Miura O
First Department of Internal Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan.
Journal of biological chemistry (UNITED STATES) Aug 9 1996, 271 (32)

p19483-8, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE

An epidermal growth factor receptor/Jak2 tyrosine kinase domain chimera induces *tyrosine* *phosphorylation* of Stat5 and transduces a growth signal in hematopoietic cells.

... 3, EGF prevented apoptosis of the transfected cells, induced dose-dependent proliferation, and supported long-term growth. EGF stimulation of the transfectants induced dose-dependent *tyrosine* *phosphorylation* of the EGFR/Jak2 chimera and Stat5, which correlated with the EGF dose dependence of cell proliferation. On the other hand, EGF did not induce *tyrosine* *phosphorylation* of other factors implicated in *cytokine* receptor signaling, including the IL-3 receptor beta subunit, *Jak* *kinases* , Stat proteins other than Stat5, Shc, Syp, and mitogen-activated protein kinases. These results suggest that the activation of Jak2 may be sufficient for transducing...

Descriptors: Chimeric Proteins--Metabolism--ME; **DNA*-Binding Proteins --Metabolism--ME; *Hematopoietic Stem Cells--Cytology--CY; *Protein-Tyrosin e Kinase--Metabolism--ME; *Receptor, Epidermal Growth Factor--Metabolism --ME; *Trans-Activators--Metabolism--ME; *Tyrosine...
; Base Sequence; Cell Division; Cell Line; Chimeric Proteins--Genetics--GE; *DNA* Primers; Epidermal Growth Factor--Metabolism--ME; Hematopoietic Stem Cells--Metabolism--ME; Molecular Sequence Data; Phosphorylation; Protein-Tyrosine Kinase--Genetics--GE; Receptor, Epidermal Growth Factor --Genetics...

Chemical Name: Janus kinase 2; (Protein-Tyrosine Kinase; (Receptor, Epidermal Growth Factor; (mammary gland-specific nuclear factor; (Chimeric Proteins; (*DNA* Primers; (*DNA*-Binding Proteins; (Trans-Activators; (Tyrosine; (Epidermal Growth Factor

6/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08849984 96366830

PDGF stimulates *tyrosine* *phosphorylation* of JAK 1 protein tyrosine kinase in human mesangial cells.

Choudhury GG; Marra F; Kiyomoto H; Abboud HE
Department of Medicine, University of Texas, Health Science Center at San Antonio, USA.

Kidney international (UNITED STATES) Jan 1996, 49 (1) p19-25, ISSN 0085-2538 Journal Code: KVB
Contract/Grant No.: DK 43988, DK, NIDDK; DK 33665, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

PDGF stimulates *tyrosine* *phosphorylation* of JAK 1 protein tyrosine kinase in human mesangial cells.

...transcription factors referred to as signal transducers and activators of transcription (STAT) has recently been identified. This group of transcription factors is activated by different *cytokines* via *tyrosine* *phosphorylation* . We studied the effect of PDGF on STATs in human mesangial cells. Using a gel retardation assay, nuclear and cytoplasmic extracts from PDGF-stimulated mesangial cells contained protein factors that bind to a *DNA* sequence representing the sis-inducible element (SIE) present in the c-fos gene promoter. These protein factors also bind to the enhancer element present in interferon-gamma responsive genes, suggesting the involvement of STAT proteins. The addition of monoclonal antibody that recognizes STAT 1 results in "supershift" of the *DNA*-protein complex stimulated by PDGF indicating the presence of STAT 1. Immunoblotting experiments with a monoclonal STAT 1 antibody revealed the presence of STAT1 alpha and STAT1 beta in mesangial cells. Since certain *cytokines* activate STATs via *tyrosine* *phosphorylation* mediated by JAK family of tyrosine kinases, we studied the effect of PDGF on *JAK* *kinases*.

Antiphosphotyrosine immunoblotting of JAK 1 immunoprecipitates from PDGF-stimulated mesangial cell lysate showed increased *tyrosine* *phosphorylation* of this tyrosine kinase. In vitro immune complex kinase assay of JAK 1 immunoprecipitates from PDGF-stimulated mesangial cell lysate revealed activation of this tyrosine...

... together, these data demonstrate that PDGF activates the transcription factor STAT 1 in mesangial cells. The data also provide the first evidence that PDGF stimulates *tyrosine* *phosphorylation* of JAK 1, the cytoplasmic tyrosine kinase stimulated by many other *cytokines* to activate transcription via STATs. These observations indicate that JAK 1 is a downstream tyrosine kinase in PDGF receptor signaling and is a candidate for...

Descriptors: *DNA*--Metabolism--ME; *Glomerular Mesangium--Enzymology--EN ; *Platelet-Derived Growth Factor--Pharmacology--PD; *Protein-Tyrosine Kinase--Metabolism--ME; Binding Sites; Cells, Cultured; *DNA*--Drug Effects --DE; Glomerular Mesangium--Drug Effects--DE; Phosphorylation--Drug Effects --DE; Protein-Tyrosine Kinase--Drug Effects--DE; Protein-Tyrosine Kinase --Genetics--GE

Chemical Name: Janus kinase 1; (Protein-Tyrosine Kinase; (Platelet-Derived Growth Factor; (*DNA*

6/3,K/3 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08788714 96382495

Inhibition of *cytokines* and JAK-STAT activation by distinct signaling pathways.

Sengupta TK; Schmitt EM; Ivashkiv LB

Department of Medicine, Hospital for Special Surgery, New York, NY 10021, USA.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Sep 3 1996, 93 (18) p9499-504, ISSN 0027-8424

Journal Code: PV3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Inhibition of *cytokines* and JAK-STAT activation by distinct signaling pathways.

An important component of *cytokine* regulation of cell growth and differentiation is rapid transcriptional activation of genes by the JAK-STAT (signal transducer and activator of transcription) signaling pathway. Ligation of *cytokine* receptors results in *tyrosine* *phosphorylation* and activation of receptor-associated Jak protein tyrosine kinases and cytoplasmic STAT transcription factors, which then translocate to the nucleus. We describe the interruption of *cytokine* triggered JAK-STAT signals by cAMP, the calcium ionophore ionomycin, and granulocyte/macrophage colony-stimulating factor. *Jak1* *kinase* activity, interleukin 6-induced gene activation, Stat3 *tyrosine* *phosphorylation*, and *DNA* -binding were inhibited, as was activation of Jak1 and Stat1 by interferon gamma. The kinetics and requirement for new RNA and protein synthesis for inhibition...

... ID (SH2-containing phosphatase 2). Our results demonstrate that crosstalk with distinct signaling pathways can inhibit JAK-STAT signal transduction, and suggest approaches for modulating *cytokine* activity during immune responses and inflammatory processes.

Descriptors: *Cytokines*--Antagonists and Inhibitors--AI; **DNA*-Binding Proteins--Metabolism--ME; *Protein-Tyrosine Kinase --Antagonists and Inhibitors--AI; *Protein-Tyrosine Kinase--Metabolism--ME; *Signal Transduction; *Trans-Activators--Metabolism--ME; *Transcription, Genetic; Blotting, Northern; Cells, Cultured; Cyclic AMP--Pharmacology--PD; Cycloheximide--Pharmacology--PD; Dactinomycin--Pharmacology--PD; *DNA* --Metabolism--ME; Enzyme Activation; Granulocyte-Macrophage Colony-Stimulat

ing Factor--Pharmacology--PD; Interferon Type II--Metabolism--ME; Interleukin-6--Antagonists and Inhibitors--AI; Ionomycin--Pharmacology--PD ...
Chemical Name: Janus kinase 1; (Janus kinase 3; (Protein-Tyrosine Kinase; (Syp protein; (Protein-Tyrosine-Phosphatase; (gamma-activated factor, 91-kD; (*Cytokines*; (*DNA-Binding Proteins*; (Interleukin-6; (Stat3 protein; (Trans-Activators; (Dactinomycin; (Ionomycin; (Cyclic AMP; (RNA; (Cycloheximide; (Interferon Type II; (Granulocyte-Macrophage Colony-Stimulating Factor; (*DNA*

6/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08771826 96282847
Convergence of signaling transduced by prolactin (PRL)/*cytokine* chimeric receptors on PRL-responsive gene transcription.
Ferrag F; Chiarenza A; Goffin V; Kelly PA
INSERM U. 344, Faculte de Medecine Necker, Paris, France.
Molecular endocrinology (UNITED STATES) Apr 1996, 10 (4) p451-60, ISSN 0888-8809 Journal Code: NGZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Convergence of signaling transduced by prolactin (PRL)/*cytokine* chimeric receptors on PRL-responsive gene transcription.
Ligand binding to *cytokine* receptors rapidly triggers *tyrosine* *phosphorylation* of Janus family tyrosine kinases (Jaks) and signal transducers and activators of transcription (Stats). Jak2 activation is mediated by PRL receptor homodimers as well as...

... that chimeric PRL receptors that contain the transmembrane and cytoplasmic domains of the IL-2R beta or beta c-chains transduce in response to PRL *tyrosine* *phosphorylation* and activation of Jak1 and Jak2, respectively. *Tyrosine* *phosphorylation* of Stat5, activation of its *DNA* -binding activity assessed in bandshift experiments using a lactogenic hormone responsive region (LHRR) probe, and transcriptional induction of a beta-casein promoter luciferase construct in stably transfected CHO cells are observed with both chimeras upon PRL stimulation. Our results demonstrate that distinct cytoplasmic domains of these *cytokine* receptors elicit convergent signaling pathways and provide evidence that beta c and IL-2R beta function as a complete signal transducer. Our data strengthen previous observations that Stat5 activation is not dependent on the activation of a specific *Jak* *kinase* and also suggest that neither Jak3 nor gamma c have a specific role in this process.
; Amino Acid Sequence; Chimeric Proteins--Biosynthesis--BI; Chimeric Proteins--Metabolism--ME; Cross-Linking Reagents; CHO Cells; Dexamethasone --Pharmacology--PD; *DNA*-Binding Proteins--Metabolism--ME; Hamsters; Luciferase--Biosynthesis--BI; Macromolecular Systems; Molecular Sequence Data; Protein-Tyrosine Kinase--Metabolism--ME; Rabbits; Rats; Receptors, Interleukin-2--Biosynthesis--BI...
Chemical Name: Luciferase; (Janus kinase 1; (Janus kinase 2; (Janus kinase 3; (Protein-Tyrosine Kinase; (mammary gland-specific nuclear factor; (Chimeric Proteins; (Cross-Linking Reagents; (*DNA*-Binding Proteins; (Macromolecular Systems; (Receptors, Interleukin-2; (Receptors, Prolactin; (Recombinant Proteins; (Trans-Activators; (Dexamethasone; (Prolactin; (Somatotropin

6/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08395556 95372363
Interleukin 2 signaling involves the phosphorylation of Stat proteins.

Frank DA; Robertson MJ; Bonni A; Ritz J; Greenberg ME
Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, MA 02115, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Aug 15 1995, 92 (17) p7779-83, ISSN 0027-8424
Journal Code: PV3
Contract/Grant No.: CA41619, CA, NCI; CA43855, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

One of the most important *cytokines* involved in immune response regulation is interleukin 2 (IL-2), a potent activator of the proliferation and function of T lymphocytes and natural killer cells...

... Jak-3, subsequent steps in the signaling pathway to the nucleus that lead to the activation of specific genes had not been characterized. Since many *cytokines* that activate *Jak* *kinases* also lead to the *tyrosine* *phosphorylation* and activation of members of the Stat family of transcription factors, the ability of IL-2 to trigger Stat phosphorylation was examined. Exposure of activated...

... SH2) domain, but otherwise are immunologically distinct from Stat1. These Stat proteins were found to translocate to the nucleus and to bind to a specific *DNA* sequence. These findings suggest a mechanism by which IL-2 binding to its receptor may activate specific genes involved in immune cell function.
Descriptors: *DNA*-Binding Proteins--Metabolism--ME; *Interleukin-2 --Pharmacology--PD; *Killer Cells, Natural--Metabolism--ME; *T-Lymphocytes --Metabolism--ME; *Trans-Activators--Metabolism--ME; Blotting, Western; *DNA*-Binding Proteins--Isolation and Purification--IP; Interferon-alpha --Pharmacology--PD; Killer Cells, Natural--Drug Effects--DE; Killer Cells, Natural--Immunology--IM; Phosphoproteins--Isolation and Purification...
Chemical Name: mammary gland-specific nuclear factor; (transcription factor Stat4; (*DNA*-Binding Proteins; (Interferon-alpha; (Interleukin-2; (Phosphoproteins; (Recombinant Proteins; (Trans-Activators; (Stat6 protein ; (Phosphotyrosine; (Tyrosine

6/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08388382 95137005
***Tyrosine* *phosphorylation* of p95Vav in myeloid cells is regulated by GM-CSF, IL-3 and steel factor and is constitutively increased by p210BCR/ABL [see comments]**
Matsuguchi T; Inhorn RC; Carlesso N; Xu G; Druker B; Griffin JD
Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, MA 02115.
EMBO journal (ENGLAND) Jan 16 1995, 14 (2) p257-65, ISSN 0261-4189
Journal Code: EMB
Contract/Grant No.: CA36167, CA, NCI
Comment in NIH Guide Grants Contracts 1995 Dec 8;24(42):1-2
Languages: ENGLISH
Document type: JOURNAL ARTICLE

***Tyrosine* *phosphorylation* of p95Vav in myeloid cells is regulated by GM-CSF, IL-3 and steel factor and is constitutively increased by p210BCR/ABL [see comments]**
... receptors and stimulation of immature hematopoietic cells by Steel factor. Monoclonal antibodies to human Vav were generated and used to examine the events which regulate *tyrosine* *phosphorylation* of p95Vav in myeloid cells. In the factor-dependent MO7e cell line, p95Vav was rapidly phosphorylated on tyrosine residues in a dose- and time-dependent...

... IL-3 and Steel factor. Introduction of the BCR/ABL oncogene into this

cell line resulted in factor-independent proliferation and constitutive phosphorylation of p95Vav. *Tyrosine* *phosphorylation* of p95Vav was also substantially increased by treatment of *cytokine*-deprived cells with the tyrosine phosphatase inhibitor sodium vanadate. Since many of the *cytokines* known to induce *tyrosine* *phosphorylation* of p95Vav are also known to activate JAK family tyrosine kinases, we looked for an interaction of p95Vav with *JAK* *kinases*. p95Vav co-precipitated with JAK2 in MO7e cells stimulated with GM-CSF, but not in unstimulated cells. Also, JAK2 was found to be constitutively associated with p95Vav in vivo when expressed at high levels in insect cells using baculovirus *vectors*. A fusion protein consisting of glutathione-S-transferase and the SH2 domain of p95Vav (GST-Vav-SH2) precipitated JAK2, suggesting that this interaction is mediated...

6/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08357696 95365357
Interleukin 12 induces *tyrosine* *phosphorylation* and activation of STAT4 in human lymphocytes.
Bacon CM; Petricoin EF 3rd; Ortaldo JR; Rees RC; Larner AC; Johnston JA; O'Shea JJ
Lymphocyte Cell Biology Section, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Aug 1 1995, 92 (16) p7307-11, ISSN 0027-8424
Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Interleukin 12 induces *tyrosine* *phosphorylation* and activation of STAT4 in human lymphocytes.
Interleukin 12 (IL-12) is an important immunoregulatory *cytokine* whose receptor is a member of the hematopoietin receptor superfamily. We have recently demonstrated that stimulation of human T and natural killer cells with IL-12 induces *tyrosine* *phosphorylation* of the Janus family tyrosine kinase JAK2 and Tyk2, implicating these kinases in the immediate biochemical response to IL-12. Recently, transcription factors known as STATs (signal transducers and activators of transcription) have been shown to be tyrosine phosphorylated and activated in response to a number of *cytokines* that bind hematopoietin receptors and activate *JAK* *kinases*. In this report we demonstrate that IL-12 induces *tyrosine* *phosphorylation* of a recently identified STAT family member, STAT4, and show that STAT4 expression is regulated by T-cell activation. Furthermore, we show that IL-12 stimulates formation of a *DNA*-binding complex that recognizes a *DNA* sequence previously shown to bind STAT proteins and that this complex contains STAT4. These data, and the recent demonstration of JAK phosphorylation by IL-12...
Descriptors: *DNA*-Binding Proteins--Metabolism--ME; *Interleukin-12 --Pharmacology--PD; *T-Lymphocytes--Metabolism--ME; *Trans-Activators --Metabolism--ME; *Tyrosine--Metabolism--ME; Base Sequence; *DNA*--Genetics --GE; Gene Expression; Killer Cells, Natural--Drug Effects--DE; Killer Cells, Natural--Immunology--IM; Killer Cells, Natural--Metabolism--ME; Molecular Sequence Data; Phosphorylation; Protein...
Chemical Name: Janus kinase 2; (Protein-Tyrosine Kinase; (transcription factor Stat4; (*DNA*-Binding Proteins; (Interleukin-12; (Proteins; (Receptors, IgG; (Trans-Activators; (tyk2 protein; (Tyrosine; (*DNA*

6/3,K/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08306713 95290118

Signaling mechanisms through *cytokine* receptors that share signal transducing receptor components.

Taga T; Kishimoto T

Institute for Molecular and Cellular Biology, Osaka University, Japan.

Current opinion in immunology (ENGLAND) Feb 1995, 7 (1) p17-23, ISSN 0952-7915 Journal Code: AH1

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

Signaling mechanisms through *cytokine* receptors that share signal transducing receptor components.

Most of the receptors for soluble factors functioning in immune and hematopoietic systems belong to the *cytokine* receptor family. These receptors often share common signal transducing receptor components with other members of the same family. Such receptors and signal transducers possess no intrinsic tyrosine kinase domain but have recently been found to be associated with members of a JAK family of cytoplasmic tyrosine kinases. The *JAK* *kinases* become activated after ligand-induced dimerization of the receptor components. This activation appears to link the cell surface receptors to the nuclear genes through *tyrosine* *phosphorylation* and activation of latent cytoplasmic transcription factors called signal transducers and activators of transcription (STATs).

Descriptors: Receptors, *Cytokine*--Chemistry--CH; *Receptors, *Cytokine*--Immunology--IM; *Signal Transduction--Immunology--IM; *DNA* -Binding Proteins--Chemistry--CH; *DNA*-Binding Proteins--Immunology--IM; Granulocyte-Macrophage Colony-Stimulating Factor--Immunology--IM; Interleuk in-6--Immunology--IM; Membrane Glycoproteins--Immunology--IM; Protein-Tyros ine Kinase--Immunology--IM; Receptors...

Chemical Name: Janus kinase 1; (Janus kinase 2; (Protein-Tyrosine Kinase; (*DNA*-Binding Proteins; (Interleukin-6; (Membrane Glycoproteins; (Receptors, *Cytokine*; (Receptors, Interleukin-2; (Stat2 protein; (Trans-Activators; (gp130 signal transducer; (Granulocyte-Macrophage Colony-Stimulating Factor

6/3,K/9 (Item 9 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08297650 95276241

***Tyrosine* *phosphorylation* and activation of JAK family tyrosine kinases by interleukin-9 in MO7E cells.**

Yin T; Yang L; Yang YC

Walther Oncology Center, Indiana University Medical Center, Indianapolis 46202, USA.

Blood (UNITED STATES) Jun 1 1995, 85 (11) p3101-6, ISSN 0006-4971 Journal Code: A8G

Contract/Grant No.: R01HL48819, HL, NHLBI; R01DK43105, DK, NIDDK

Languages: ENGLISH

Document type: JOURNAL ARTICLE

***Tyrosine* *phosphorylation* and activation of JAK family tyrosine kinases by interleukin-9 in MO7E cells.**

Interleukin-9 (IL-9) is a T-cell-derived multifunctional *cytokine* that can stimulate the proliferation of a human megakaryocytic leukemia cell line, MO7E. Previous studies suggested that protein *tyrosine* *phosphorylation* may be involved in IL-9 signaling pathways. However, tyrosine kinases activated by IL-9 have not been identified. In this report we show that IL-9 induces *tyrosine* *phosphorylation* and activation of the JAK family tyrosine kinases including JAK1, JAK3, and Tyk2. The kinetic studies indicate that *tyrosine* *phosphorylation* and activation of *JAK* *kinases* induced by IL-9 occurred within 1 minute, peaked by 5 to 10 minutes, and persisted at least for 45 minutes. Furthermore, we show that ...

... rapidly tyrosine phosphorylated following IL-9 treatment. Gel shift assays confirm that nuclear extracts from MO7E cells stimulated with IL-9 specifically interact with a *DNA* element termed gamma activated site. These results suggest that actions of IL-9 may, in part, be mediated through *JAK* *kinase*-Stat signaling cascades.

; Base Sequence; *DNA*-Binding Proteins--Metabolism--ME; Enzyme Activation--Drug Effects--DE; Gene Expression Regulation, Leukemic--Drug Effects--DE; Leukemia, Megakaryocytic, Acute--Pathology--PA; Molecular Sequence Data; Phosphorylation...

Chemical Name: Janus kinase 1; (Janus kinase 3; (Protein-Tyrosine Kinase; (gamma-activated factor, 91-kD; (*DNA*-Binding Proteins; (Interleukin-9; (Neoplasm Proteins; (Proteins; (Trans-Activators; (tyk2 protein

6/3,K/10 (Item 10 from file: 155)

08256007 95195208

Interleukin-5 signaling in human eosinophils involves JAK2 tyrosine kinase and Stat1 alpha.

van der Bruggen T; Caldenhoven E; Kanters D; Coffer P; Raaijmakers JA; Lammers JW; Koenderman L

Department of Pulmonary Diseases, University Hospital, Utrecht, The Netherlands.

Blood (UNITED STATES) Mar 15 1995, 85 (6) p1442-8, ISSN 0006-4971
Journal Code: A8G

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Signaling by a wide variety of *cytokines* , including interferons, interleukins, and growth factors, involves activation of *JAK* *kinases* and Stat (Signal transducers and activators of transcription) proteins. At present, not much is known about the molecular mechanisms by which interleukin-5 (IL-5...

... target cells for IL-5 and were used here to study IL-5 signaling in a primary human cell. IL-5 induced rapid and transient *tyrosine* *phosphorylation* of JAK2. Moreover, IL-5 induced at least two *DNA* -binding complexes, using nuclear extracts from normal human eosinophils and the IL-6/interferon-gamma response element of the ICAM-1 promoter (ICAM-1 pIRE) in an electromobility shift assay. From supershift experiments it was concluded that one *DNA*-binding complex contained Stat1 alpha, probably as a homodimer. Both *DNA*-binding complexes were inhibited by a phosphotyrosine antibody (4G10), suggesting that *tyrosine* *phosphorylation* is required for complex formation. IL-3 and granulocyte-macrophage colony-stimulating factor induced, similar to IL-5, two *DNA* -binding complexes in human eosinophils, including Stat1 alpha. These data show for the first time that molecular mechanisms of IL-5 signaling in human eosinophils involve members of the *JAK* *kinase* family as well as members of the Stat family.

Descriptors: *DNA*-Binding Proteins--Physiology--PH; *Eosinophils--Drug Effects--DE; *Interleukin-5--Pharmacology--PD; *Trans-Activators--Physiology--PH; Base Sequence; *DNA*--Metabolism--ME; Eosinophils--Metabolism--ME; Intercellular Adhesion Molecule-1--Genetics--GE; Interferon Type II --Pharmacology--PD; Molecular Sequence Data; Phosphorylation; Protein-Tyrosine Kinase--Physiology--PH

Chemical Name: Janus kinase 2; (Protein-Tyrosine Kinase; (gamma-activated factor, 91-kD; (*DNA*-Binding Proteins; (Interleukin-5; (Trans-Activators; (Intercellular Adhesion Molecule-1; (Interferon Type II; (*DNA*

6/3,K/11 (Item 11 from file: 155)

08199194 94181577

Activation of *JAK2* *kinase* mediated by the interleukin 6 signal transducer gp130.

Narazaki M; Witthuhn BA; Yoshida K; Silvennoinen O; Yasukawa K; Ihle JN; Kishimoto T; Taga T

Institute for Molecular and Cellular Biology, Osaka University, Japan.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Mar 15 1994, 91 (6) p2285-9, ISSN 0027-8424 Journal Code: PV3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Activation of *JAK2* *kinase* mediated by the interleukin 6 signal transducer gp130.

... associated signal transducer, gp130, is shared by receptor complexes for leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, and interleukin 11. We show here that *JAK2* *kinase* is rapidly tyrosine phosphorylated in mouse embryonic stem cells whose pluripotentiality is maintained only by gp130-sharing *cytokines* after stimulation that is known to induce gp130 homodimerization. JAK1 is also tyrosine phosphorylated, but to a lesser extent, under the same conditions. Comparable results...

... pro-B-cell line-derived transfectants expressing gp130, the former of which differentiate into macrophages after stimulation of gp130 and the latter of which initiate *DNA* synthesis. gp130-dimerizing stimulus upregulates kinase activity of JAK2 as revealed by immunocomplex kinase assay. Deletion or point mutation in the membrane-proximal cytoplasmic motifs in gp130 that are conserved in the hemopoietic *cytokine* receptor family results in the loss of *tyrosine* *phosphorylation* of JAK2, which coincides with the lack of signal transducing capability of gp130 mutants.

6/3,K/12 (Item 12 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08169158 95050498

Differential *tyrosine* *phosphorylation* of JAK1, JAK2, and STAT1 by growth hormone and interferon-gamma in IM-9 cells.

Silva CM; Lu H; Weber MJ; Thorner MO

Division of Endocrinology and Metabolism, University of Virginia Health Sciences Center, Charlottesville 22908.

Journal of biological chemistry (UNITED STATES) Nov 4 1994, 269 (44) p27532-9, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: CA39076, CA, NCI; DK-08942, DK, NIDDK; DK-32632, DK, NIDDK; +

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Differential *tyrosine* *phosphorylation* of JAK1, JAK2, and STAT1 by growth hormone and interferon-gamma in IM-9 cells.

Both the growth hormone (GH) and interferon gamma (IFN gamma) receptors are members of the *cytokine* receptor family that activate *tyrosine* *phosphorylation* despite the lack of a tyrosine kinase domain. Recently, the Janus kinase (JAK) family of tyrosine kinases have been shown to play an integral role in intracellular signaling by the *cytokine* receptors. We demonstrate that, in the human IM-9 lymphocyte, both JAK1 and JAK2 are tyrosine-phosphorylated in response to IFN gamma, whereas only JAK2 is tyrosine-phosphorylated in response to GH. Furthermore, dimerization of the GH receptor appears to be necessary for GH stimulated *tyrosine* *phosphorylation* of JAK2. We provide two lines of evidence that the *JAK2* *kinases* can be regulated independently by GH and IFN gamma in IM-9 cells: 1) desensitization of JAK2 to GH stimulation does not affect the IFN gamma stimulated *tyrosine* *phosphorylation* of JAK2; and 2) JAK2 *tyrosine* *phosphorylation* by GH and IFN gamma is additive to that seen

with either hormone alone. Furthermore, we demonstrate that although IFN gamma activates the *tyrosine* *phosphorylation* of the p91 signal transducer and activator of transcription (STAT1) in IM-9 cells, GH does not. GH does activate the *tyrosine* *phosphorylation* of a 93-kDa protein that appears to be distinct from STAT1.

Descriptors: *DNA*-Binding Proteins--Metabolism--ME; *Interferon Type II --Pharmacology--PD; *Protein-Tyrosine Kinase--Metabolism--ME; *Somatotropin --Pharmacology--PD; *Trans-Activators--Metabolism--ME

Chemical Name: Janus kinase 1; (Janus kinase 2; (Protein-Tyrosine Kinase; (gamma-activated factor, 91-kD; (interferon gamma receptor; (*DNA*-Binding Proteins; (Receptors, Interferon; (Receptors, Somatotropin; (Trans-Activators; (Phosphotyrosine; (Tyrosine; (Interferon Type II; (Somatotropin

6/3,K/13 (Item 13 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08164478 94316659

Prolactin activates the interferon-regulated p91 transcription factor and the *Jak2* *kinase* by *tyrosine* *phosphorylation*.

David M; Petricoin EF 3rd; Igarashi K; Feldman GM; Finbloom DS; Larner AC

Division of Cytokine Biology, Center for Biologics Evaluation and Research, Bethesda, MD 20892.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Jul 19 1994, 91 (15) p7174-8, ISSN 0027-8424

Journal Code: PV3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Prolactin activates the interferon-regulated p91 transcription factor and the *Jak2* *kinase* by *tyrosine* *phosphorylation*.

The prolactin (PRL) receptor is a member of the family of *cytokine* receptors that lack intrinsic tyrosine kinase activity but contain two conserved cysteines in their N-terminal regions and a WSXWS motif adjacent to their transmembrane domains. In a manner similar to the interferons (IFNs), exposure of cells to PRL results in *tyrosine* *phosphorylation* of several cellular proteins and the rapid transcriptional induction of the IFN regulatory factor 1 gene. In this communication, we demonstrate that treatment of rat...

... regulatory factor 1 gene. This enhancer has been shown to be required for IFN-gamma-activated expression of this gene. PRL-induced assembly of the *DNA* binding complex, PRL-stimulated factor, required *tyrosine* *phosphorylation* . PRL-stimulated factor contained at least one protein that was antigenically similar to the p91 transcription factor, a component of several transcription complexes required for *cytokine*-activated gene expression. PRL not only induced the *tyrosine* *phosphorylation* of p91 but also induced *tyrosine* *phosphorylation* of Jak2, a tyrosine kinase required for IFN-gamma-activated gene expression. These results provide evidence for a signaling mechanism, some of whose components are...

Descriptors: *DNA*-Binding Proteins--Metabolism--ME; *Interferons --Physiology--PH; *Prolactin--Physiology--PH; *Protein-Tyrosine Kinase --Metabolism--ME; *Transcription Factors--Metabolism--ME; Base Sequence; Cell Line; *DNA*; Enzyme Activation; Mice; Molecular Sequence Data; Phosphorylation; Rats; Tumor Cells, Cultured; Tyrosine--Metabolism--ME

Chemical Name: Janus kinase 2; (Protein-Tyrosine Kinase; (gamma-activated factor, 91-kD; (*DNA*-Binding Proteins; (Transcription Factors; (Tyrosine; (Prolactin; (*DNA*; (Interferons

6/3,K/14 (Item 1 from file: 73)

DIALOG(R)File 73:EMBASE

05890807 EMBASE No: 1994299531

Erythropoietin and interleukin-2 activate distinct *JAK* *kinase* family members

Barber D.L.; D'Andrea A.D.
Pediatric Oncology, Dana-Farber Cancer Institute, 44 Binney St.,Boston, MA 02115 United States
Molecular and Cellular Biology (MOL. CELL. BIOL.) (United States) 1994 , 14/10 (6506-6514)
CODEN: MCEBD ISSN: 0270-7306
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Erythropoietin and interleukin-2 activate distinct *JAK* *kinase* family members

The erythropoietin (EPO) receptor and the interleukin-2 (IL-2) receptor beta-chain subunit are members of the *cytokine* receptor superfamily. They have conserved primary amino acid sequences in their cytoplasmic domains and activate phosphorylation of common substrates, suggesting common biochemical signaling mechanisms. We...
...and IL-2. CTLL-EPO-R cells demonstrated similar growth kinetics in EPO and IL-2. Stimulation with EPO resulted in the rapid, dose-dependent *tyrosine* *phosphorylation* of JAK2. In contrast, stimulation with IL-2 or the related *cytokine* IL-4 resulted in the rapid, dose-dependent *tyrosine* *phosphorylation* of JAK1 and an additional 116-kDa protein. This 116-kDa protein was itself immunoreactive with a polyclonal antiserum raised against JAK2 and appears to be a novel member of the *JAK* *kinase* family. Immune complex kinase assays confirmed that IL-2 and IL-4 activated JAK1 and EPO activated JAK2. These results demonstrate that multiple biochemical pathways are capable of conferring a mitogenic signal in CTLL-EPO-R cells and that the EPO and IL-2 receptors interact with distinct *JAK* *kinase* family members within the same cellular background.
DRUG DESCRIPTORS:
cell surface receptor; *cytokine* receptor; complementary *dna*; interleukin 4; monoclonal antibody; polyclonal antibody
?ds

```
Set     Items   Description
S1        759   (JAK? (W) KINASE?)
S2        261   S1 AND (DNA OR VECTOR?)
S3        112   S2 AND (TYROSINE (W) PHOSPHORYLATION)
S4         65   S3 AND (CYTOKINE?)
S5         34   RD (unique items)
S6         14   S5 NOT PY>1996
?s (JAK? (w) kinase (w) peptide?)
          19983  JAK?
         445413  KINASE
         709119  PEPTIDE?
      S7      0  (JAK? (W) KINASE (W) PEPTIDE?)
?s s1 and review?
            759  S1
        1415389  REVIEW?
      S8     46  S1 AND REVIEW?
?rd
...completed examining records
      S9     37  RD (unique items)
?s s9 and (cytokine and (tyrosine (w) phosphorylation))
             37  S9
         151891  CYTOKINE
         210595  TYROSINE
         224543  PHOSPHORYLATION
          29972  TYROSINE(W)PHOSPHORYLATION
     S10      9  S9 AND (CYTOKINE AND (TYROSINE (W) PHOSPHORYLATION))
?t s10/3,k/all
```

10/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10435328 20309845

IL-3 signaling and the role of Src kinases, JAKs and STATs: a covert liaison unveiled.

Reddy EP; Korapati A; Chaturvedi P; Rane S

Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, 3307 N Broad Street, Philadelphia, Pennsylvania, PA 19140, USA.

Oncogene (ENGLAND) May 15 2000, 19 (21) p2532-47, ISSN 0950-9232 Journal Code: ONC

Contract/Grant No.: CA98239, CA, NCI; ES09225, ES, NIEHS

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC

... cell types and aberrations in these pathways is an underlying cause for diseases such as cancer. Over the past several years, downstream events initiated upon *cytokine*/growth factor stimulation have been a major focus of biomedical research. As a result, several key concepts have emerged allowing a better understanding of the complex signaling processes. A group of novel transcription factors, termed signal transducers and activators of transcription (STATs) appear to orchestrate the downstream events propagated by *cytokine* /growth factor interactions with their cognate receptors. Until recently, the JAK proteins were considered to be the tyrosine kinases, which dictated the levels of phosphorylation...

... evidence has accumulated which indicates that at least some of the STAT protein activation may be mediated by members of the Src gene family following *cytokine* /growth factor stimulation. Studies have demonstrated that the Src-family of tyrosine kinases can phosphorylate and activate certain STAT proteins, in lieu of *JAK* *kinases*. In such a scenario, *JAK* *kinases* may be more crucial to phosphorylation of the *cytokine* /growth factor receptors and in the process create docking sites on the receptors for binding of SH2-containing proteins such as STATs, Src-kinases and other signaling intermediates. *Tyrosine* *phosphorylation* and activation of STAT proteins can be achieved either by JAKs or Src-kinases depending on the nature of STAT that is being activated. This forms the basis for the JAK-Src-STAT model proposed in this *review*. The concerted action of *JAK* *kinases* , members of the Src-kinase family and STAT proteins, leads to cell proliferation and cell survival, the end-point of the *cytokine*/growth factor stimulus. Oncogene (2000).

10/3,K/2 (Item 2 from file: 155)

09589245 98289856

Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice.

Bole-Feysot C; Goffin V; Edery M; Binart N; Kelly PA

INSERM Unite 344-Endocrinologie Moleculaire, Faculte de Medecine Necker, Paris, France.

Endocrine reviews (UNITED STATES) Jun 1998, 19 (3) p225-68, ISSN 0163-769X Journal Code: EIK

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

... of hormones that probably resulted from the duplication of an ancestral gene. The PRLR is also a member of a larger family, known as the *cytokine* class-1 receptor superfamily, which currently has more than 20 different members. PRLRs or binding sites are widely distributed throughout the body. In fact, it...

... molecules of receptor. The PRLR contains no intrinsic tyrosine kinase cytoplasmic domain but associates with a cytoplasmic tyrosine kinase, JAK2.

Dimerization of the receptor induces *tyrosine* *phosphorylation* and activation of the *JAK* *kinase* followed by phosphorylation of the receptor. Other receptor-associated kinases of the Src family have also been shown to be activated by PRL. One major...

... by which to look for effects activated only by PRL or other lactogenic hormones. On the other hand, many of the effects reported in this *review* may be shared with other hormones, cytokines, or growth factors and thus will be more difficult to study. (ABSTRACT TRUNCATED)

10/3,K/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10693107 EMBASE No: 2000182248
The Jak-STAT pathway
Imada K.; Leonard W.J.
W.J. Leonard, Department of Hematology/Oncology, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharamachi, Sakyo-ku, Kyoto 606-8507 Japan
AUTHOR EMAIL: wjl@helix.nih.gov
Molecular Immunology (MOL. IMMUNOL.) (United Kingdom) 2000, 37/1-2 (1-11)
CODEN: IMCHA ISSN: 0161-5890
PUBLISHER ITEM IDENTIFIER: S0161589000000183
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 127

A variety of important cellular functions are regulated by cytokines. The Jak-STAT pathway is one of the important signaling pathways downstream of *cytokine* receptors. Following binding of a ligand to its cognate receptor, receptor-associated Jaks are activated. STAT proteins are then in turn activated by *tyrosine* *phosphorylation* by *Jak* *kinases*, allowing their dimerization and subsequent translocation into the nucleus, where they modulate expression of target genes. Indispensable functions of Jaks and STATs in *cytokine* signaling in vivo have been revealed through knockout mouse studies. Moreover, the recent discovery of the CIS/SOCS/JAB/SSI family of inhibitors has contributed...
DRUG DESCRIPTORS:
cytokine receptor--endogenous compound--ec; *cytokine*--endogenous compound--ec; transcription factor; STAT1 protein--endogenous compound--ec; STAT3 protein--endogenous compound--ec; STAT4 protein--endogenous compound --ec; STAT5 protein--endogenous compound--ec...
MEDICAL DESCRIPTORS:
...binding; protein phosphorylation; combined immunodeficiency; protein structure; dimerization; gene targeting; gene expression; knockout mouse; in vivo study; nonhuman; mouse; animal experiment; animal model; controlled study; *review*; priority journal

10/3,K/4 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07246554 EMBASE No: 1998133762
Molecular mechanisms of inflammation: Interleukin-6-type *cytokine* signaling through the Jak/STAT pathway
MOLEKULARE MECHANISMEN DER ENTZUNDUNG: SIGNALTRANSDUKTION VON INTERLEUKIN-6-TYP-ZYTOKINEN UBER DEN JAK/STAT-WEG
Heinrich P.C.; Behrmann I.; Graeve L.; Grotzinger J.; Haan S.; Horn F.; Horsten U.; Kerr I.; May P.; Muller-Newen G.; Terstegen L.; Thiel S.
Dr. P.C. Heinrich, Institut fur Biochemie, Rheinisch-Westfalische Tech. Hoch., Pauwelsstrasse 30, D-52057 Aachen Germany
Nieren- und Hochdruckkrankheiten (NIEREN- HOCHDRUCKKR.) (Germany) 1998

, 27/3 (123-131)
CODEN: NIHOD ISSN: 0300-5224
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH; GERMAN
NUMBER OF REFERENCES: 17

Molecular mechanisms of inflammation: Interleukin-6-type *cytokine* signaling through the Jak/STAT pathway

...6, gp80, and gp130 results in the activation of the Jak family tyrosine kinases Jak1, Jak2, and Tyk2. Using mutant fibrosarcoma cells lacking the different *Jak* *kinases*, Jak1 was found to play a major role in the *tyrosine* *phosphorylation* of gp130 and activation of the transcription factors STAT1 and STAT3. Out of the 6 tyrosine residues present in the cytoplasmic region of gp130 we...

...tyrosine residues are able to activate STAT3, the last 2 tyrosine residues lead to STAT1 activation, whereas STAT5 could not be activated via gp130. After *tyrosine* *phosphorylation* the STAT factors homo- or hetero-dimerize and translocate to the nucleus where they bind to response elements of IL-6 target genes. The IL...
DRUG DESCRIPTORS:
**cytokine*; *interleukin 6; *interleukin 6 receptor
MEDICAL DESCRIPTORS:
sarcoma cell; hepatoma cell; hela cell; endocytosis; internalization; protein phosphorylation; signal transduction; receptor binding; human; nonhuman; human cell; animal cell; *review*

10/3,K/5 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06946766 EMBASE No: 1997231283
***Cytokine* receptor signal transduction through Jak tyrosine kinases and Stat transcription factors**
Silvennoinen O.; Saharinen P.; Paukku K.; Takaluoma K.; Kovanen P.
O. Silvennoinen, Institute of Medical Technology, University of Tampere, P.O. Box 607, SF-33101 Tampere Finland
APMIS (APMIS) (Denmark) 1997, 105/7 (497-509)
CODEN: APMSE ISSN: 0903-4641
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 67

***Cytokine* receptor signal transduction through Jak tyrosine kinases and Stat transcription factors**

Cytokines are the principal regulators of cell proliferation and differentiation of hematopoietic cells and these responses are initiated through activation of hematopoietic *cytokine* receptors. Although the receptor intracellular domains lack any kinase domains, activation of *cytokine* receptors lead to rapid induction of *tyrosine* *phosphorylation*. Recently, *cytokine* receptors have been shown to associate with and activate members of the cytoplasmic Jak tyrosine kinase family. Activation of *Jak* *kinases* leads to phosphorylation of several signaling proteins and thereby couples ligand-mediated receptor stimulation to activation of intracellular signaling pathways. The best characterized substrates for Jaks are the Stat transcription factors, which are crucial mediators of *cytokine*-mediated gene responses, and, particularly, central determinants for the specificity in *cytokine* responses.
DRUG DESCRIPTORS:
**cytokine* receptor--endogenous compound--ec; *protein tyrosine kinase --endogenous compound--ec; *transcription factor--endogenous compound--ec
MEDICAL DESCRIPTORS:
animal cell; human; human cell; nonhuman; priority journal; *review*

10/3,K/6 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

06929724 EMBASE No: 1997214203
Interleukin-5. Immunological functions and therapeutic potential of a putative antagonist
Takatsu K.
Dr. K. Takatsu, Department of Immunology, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108 Japan
BioDrugs (BIODRUGS) (New Zealand) 1997, 8/1 (33-45)
CODEN: BIDRF ISSN: 1173-8804
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 96

...5) is an interdigitating homodimeric glycoprotein and features the 4-alpha-helical-bundle motif which is conserved among several haemopoietic cytokines. It is a potent *cytokine* which induces proliferation and differentiation of activated B cells and induces eosinophil production and activation. IL-5 acts on target cells by binding to its...

...interleukin-3 and granulocyte-macrophage colony-stimulating factor. The betac chain is indispensable for signal transduction. Both subunits contain motifs conserved among the superfamily of *cytokine* receptors. Stimulation of cells by IL-5 induces rapid *tyrosine* *phosphorylation* of various cellular proteins, including the betac chain, and activates the Bruton tyrosine (Btk) and *JAK2* *kinases*. The cytoplasmic domain of the betac chain and the membraneproximal proline-rich sequence of the cytoplasmic domain of the alpha chain are both essential for the IL-5-induced proliferative response, for expression of nuclear proto-oncogenes and for activation of the Btk and *JAK2* *kinases*. B cells from X-linked immunodeficient (XID) mice, which have an abnormality of Btk and lack functionally mature B cells, including CD5+ B cells, show...
DRUG DESCRIPTORS:
acetylcholine--pharmacology--pd; cell protein--endogenous compound--ec; *cytokine*--endogenous compound--ec; *cytokine* antibody--pharmacology--pd; *cytokine* receptor--endogenous compound--ec; glycoprotein--endogenous compound--ec; protein tyrosine kinase--endogenous compound--ec; tyrosine; unclassified drug
MEDICAL DESCRIPTORS:
...hypereosinophilic syndrome--etiology--et; immune deficiency--etiology --et; inflammation--etiology--et; nonhuman; pathophysiology; priority journal; protein domain; protein phosphorylation; protein structure; proto oncogene; receptor binding; *review*; signal transduction; target cell; tissue level

10/3,K/7 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

06230529 EMBASE No: 1995266813
Structure and function of IL-5 receptor
Takatsu K.
Department of Immunology, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai,Minato-ku, Tokyo 108 Japan
Yakugaku Zasshi (YAKUGAKU ZASSHI) (Japan) 1995, 115/8 (570-583)
CODEN: YKKZA ISSN: 0031-6903
DOCUMENT TYPE: Journal; Review
LANGUAGE: JAPANESE SUMMARY LANGUAGE: ENGLISH; JAPANESE

...different polypeptide chains, alpha and beta. The alpha chain is a membrane-penetrated glycoprotein that specifically binds IL-5 and retains

features common to the *cytokine* receptor superfamily. The beta chain by itself does not bind IL-5, but it can convert the low affinity IL-5R into the high affinity...

...5-induced proliferative response, expression of nuclear proto- oncogenes such as c-jun, c-fos and c-myc, and activation of Bruton's tyrosine and *JAK2* *kinases*. Furthermore, JAK2 activation correlates with proline residues in Pr-Pro-X-Pro motif in the cytoplasmic domain of IL-5Ralpha. These results indicate that activation of JAK2 and its substrate is critical to coupling IL-5-induced *tyrosine* *phosphorylation* and ultimately mitogenesis. I will discuss about molecular mechanisms of IL-5 signaling and B cell defect in X-linked immunodeficient mice in relation to ...

DRUG DESCRIPTORS:
*interleukin receptor; *cd5 antigen--endogenous compound--ec; **cytokine*; *interleukin 5--pharmacology--pd; *proline--endogenous compound--ec
MEDICAL DESCRIPTORS:
animal cell; gene expression; lymphocyte proliferation; mouse; nonhuman; proto oncogene; receptor affinity; *review*; X linked agammaglobulinemia

10/3,K/8 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06070266 EMBASE No: 1995100732
Signaling mechanisms through *cytokine* receptors that share signal transducing receptor components
Taga T.; Kishimoto T.
Institute Molecular Cellular Biology, Osaka University, 1-3 Yamada-oka,Suita, Osaka 565 Japan
Current Opinion in Immunology (CURR. OPIN. IMMUNOL.) (United Kingdom) 1995, 7/1 (17-23)
CODEN: COPIE ISSN: 0952-7915
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Signaling mechanisms through *cytokine* receptors that share signal transducing receptor components

Most of the receptors for soluble factors functioning in immune and hematopoietic systems belong to the *cytokine* receptor family. These receptors often share common signal transducing receptor components with other members of the same family. Such receptors and signal transducers possess no intrinsic tyrosine kinase domain but have recently been found to be associated with members of a JAK family of cytoplasmic tyrosine kinases. The *JAK* *kinases* become activated after ligand-induced dimerization of the receptor components. This activation appears to link the cell surface receptors to the nuclear genes through *tyrosine* *phosphorylation* and activation of latent cytoplasmic transcription factors called signal transducers and activators of transcription (STATs).
DRUG DESCRIPTORS:
**cytokine* receptor
MEDICAL DESCRIPTORS:
cytoplasm; dimerization; hematopoietic system; immune system; ligand binding; mouse; nonhuman; protein phosphorylation; *review*; signal transduction

10/3,K/9 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

05879468 EMBASE No: 1994286002
***Cytokine* receptors and signal transduction**
TRANSDUCTION DU SIGNAL PAR LES RECEPTEURS DE CYTOKINES

Dusanter-Fourt I.; Mayeux P.; Gisselbrecht S.
Inserm U.363, ICGM, Hopital Cochin, 27, Rue du
Faubourg-Saint-Jacques,75014 Paris France
Medecine/Sciences (MED. SCI.) (France) 1994, 10/8-9 (825-835)
CODEN: MSMSE ISSN: 0767-0974
DOCUMENT TYPE: Journal; Review
LANGUAGE: FRENCH SUMMARY LANGUAGE: FRENCH; ENGLISH

***Cytokine* receptors and signal transduction**

...regulation of immune responses. These effects are mediated through the high affinity binding of cytokines to specific cell surface receptors. Cloning of the cDNAs encoding *cytokine* receptors has revealed that most of them display common structural features in their extracellular domain and do not contain kinase consensus sequences in their cytoplasmic region. This rapidly growing *cytokine* receptor superfamily includes not only hematopoietin receptors but also receptors for growth hormone (GH), prolactin and the ciliary neurotrophic factor (CNTF). Unlike growth factor receptors with intrinsic tyrosine kinase activity, *cytokine* receptors are often composed of several subunits. Cytokines mediating similar effects on the same target cells have been shown to share a common receptor chain...

...biological activities on T cells like IL2, IL4 and IL7 also share a common chain and inherited mutations of the chain common to these three *cytokine* receptors are responsible for the human X linked severe combined immunodeficiency syndrome (XSCID). Although none of the cytoplasmic domains of *cytokine* receptors contains a tyrosine kinase motif, stimulation of target cells with cytokines induces the *tyrosine* *phosphorylation* of specific cellular proteins, suggesting that cytoplasmic tyrosine kinases interact with *cytokine* receptors. Several tyrosine kinases of the Src family are known to be activated by *cytokine* receptors. Binding of Lck to the cytoplasmic domain of the IL2 receptor b chain occurs in a region of the receptor also responsible for Ras...

...for IL2-induced proliferation. More recently, it was shown that cytokines activate tyrosine kinases of the Jak family which interact with a region of the *cytokine* receptors proximal to the membrane and required for mitogenesis. This family of tyrosine kinases is involved in IFNa and g signal transduction, phosphorylating cytoplasmic transcription...
...and induce the expression of IFN responsive gene. However, cytokines such as erythropoietin, IL3, GH and prolactin, exerting quite different biological activities, all activate the *Jak2* *kinase*. Biological specificity may depend on the substrate specificity of the *Jak* *kinase* according to the cell type, on the activation of other unknown *Jak* *kinases* or of other tyrosine kinases, and/or on the activation of other signalling pathways such as Ras/MAP kinase phosphatidyl inositol 3' kinase and their...
DRUG DESCRIPTORS:
**cytokine* receptor; *erythropoietin receptor; *growth factor receptor; * colony stimulating factor; **cytokine*
MEDICAL DESCRIPTORS:
human; molecular cloning; nonhuman; protein family; protein phosphorylation ; receptor binding; *review*; signal transduction
?ds

Set	Items	Description
S1	759	(JAK? (W) KINASE?)
S2	261	S1 AND (DNA OR VECTOR?)
S3	112	S2 AND (TYROSINE (W) PHOSPHORYLATION)
S4	65	S3 AND (CYTOKINE?)
S5	34	RD (unique items)
S6	14	S5 NOT PY>1996
S7	0	(JAK? (W) KINASE (W) PEPTIDE?)
S8	46	S1 AND REVIEW?
S9	37	RD (unique items)
S10	9	S9 AND (CYTOKINE AND (TYROSINE (W) PHOSPHORYLATION))

```
?s s1 and (cDNA or gene)
            759  S1
         212741  CDNA
        1565510  GENE
     S11     310  S1 AND (CDNA OR GENE)
?rd
...examined 50 records  (50)
...examined 50 records  (100)
...examined 50 records  (150)
...examined 50 records  (200)
...examined 50 records  (250)
...examined 50 records  (300)
...completed examining records
     S12     167  RD (unique items)
?s s12 and (JAK1 or JAK2 or JAK3 or TYK2)
            167  S12
           1206  JAK1
           2412  JAK2
            855  JAK3
            680  TYK2
     S13     112  S12 AND (JAK1 OR JAK2 OR JAK3 OR TYK2)
?s s13 not py>1993
            112  S13
        9113356  PY>1993
     S14       3  S13 NOT PY>1993
?t s14/3,k/all
```

14/3,K/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

07790550 94077184

Interferon-induced nuclear signalling by Jak protein tyrosine kinases.

Silvennoinen O; Ihle JN; Schlessinger J; Levy DE
Kaplan Comprehensive Cancer Center, New York, New York.

Nature (ENGLAND) Dec 9 1993, 366 (6455) p583-5, ISSN 0028-0836
Journal Code: NSC
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Interferons IFN-alpha/beta and IFN-gamma act through independent cell-surface receptors, inducing *gene* expression through tyrosine phosphorylation of cytoplasmic transcription factors . IFN-alpha stimulates phosphorylation and nuclear localization of the 84/91K and 113K subunits of latent ISGF3 (interferon-stimulated *gene* factor 3), which combine with the 48K DNA-binding subunit to bind regulatory elements of IFN-alpha-responsive genes. IFN-gamma activates p91 alone, inducing IFN-gamma-responsive genes through a distinct DNA element. Genetic complementation studies implicated the tyrosine kinase *Tyk2* in IFN-alpha signalling and, more recently, the related *Jak2* *kinase* in IFN-gamma signalling. We now present biochemical evidence for Jak-family kinase involvement in IFN signal transduction. *Jak1* was activated in response to IFN-alpha and IFN-gamma; *Jak2* responded exclusively to IFN-gamma. Overexpression of either *Jak1* or *Jak2* stimulated p91 DNA-binding activity and p91-dependent transcription. Overexpression also activated endogenous *Jak* *kinases*, suggesting that interactions between *Jak* *kinases* are required during interferon signalling.

; Cell Line; Cell Nucleus--Drug Effects--DE; Chickens; Enzyme Activation; *Gene* Expression; Kinetics; Mice; Transcription, Genetic; Transfection; Tyrosine--Analogs and Derivatives--AA; Tyrosine--Analysis--AN; Tyrosine --Metabolism--ME; 3T3 Cells

14/3,K/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

07594054 93345011

***JAK2* associates with the erythropoietin receptor and is tyrosine phosphorylated and activated following stimulation with erythropoietin.**

Witthuhn BA; Quelle FW; Silvennoinen O; Yi T; Tang B; Miura O; Ihle JN
Department of Biochemistry, St. Jude Children's Research Hospital, Memphis, Tennessee 38105.

Cell (UNITED STATES) Jul 30 1993, 74 (2) p227-36, ISSN 0092-8674 Journal Code: CQ4
Contract/Grant No.: P30 CA21765, CA, NCI; RO1 DK42932, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

***JAK2* associates with the erythropoietin receptor and is tyrosine phosphorylated and activated following stimulation with erythropoietin.**

... receptor (EPOR). Although EPOR is a member of the cytokine receptor superfamily and lacks a kinase domain, EPO induces tyrosine phosphorylation, which is correlated with *gene* transcription and mitogenesis. Here we demonstrate that EPO induces tyrosine phosphorylation of *JAK2* *kinase* and activates its in vitro autophosphorylation. Using EPOR mutants, phosphorylation and activation of kinase activity correlate with the induction of mitogenesis. Furthermore, *JAK2* physically associates with a membrane-proximal region of the EPOR cytoplasmic domain that is required for biological activity. The results support the hypothesis that *JAK2* is the kinase that couples EPO binding to tyrosine phosphorylation and mitogenesis.

14/3,K/3 (Item 3 from file: 155)

07583505 93322747

Molecular cloning of the murine *JAK1* protein tyrosine kinase and its expression in the mouse central nervous system.

Yang X; Chung D; Cepko CL
Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115.

Journal of neuroscience (UNITED STATES) Jul 1993, 13 (7) p3006-17, ISSN 0270-6474 Journal Code: JDF
Contract/Grant No.: EY06361-01, EY, NEI; EY08064, EY, NEI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Molecular cloning of the murine *JAK1* protein tyrosine kinase and its expression in the mouse central nervous system.

... clone protein tyrosine kinases that may play potential roles in the development of the mammalian CNS. Using one PCR clone to screen a mouse eye *cDNA* library, a full-length *cDNA* of a cytoplasmic tyrosine kinase, the homolog of human *JAK1*, was obtained. The murine *JAK1* *kinase* belongs to a new family of cytoplasmic kinases that contain two tandem catalytic domains. Northern analyses indicated that murine *JAK1* mRNA is expressed in a variety of tissues and cell lines. In the adult mouse eye, in situ hybridization and immunohistochemistry showed that *JAK1* mRNA and protein were expressed in the retinal ganglion cell layer and the inner part of the inner nuclear layer, presumably in amacrine cells. *JAK1* protein was also detected in horizontal cells and in the two synaptic layers of the adult retina. During retinal development, *JAK1* protein was first detected in retinal ganglion cells and in their axons as early as embryonic day 14. Expression of *JAK1* protein in amacrine cells and horizontal cells occurred only postnatally. This pattern of expression was also observed in the chick retina, suggesting an evolutionarily conserved function of *JAK1* *kinase* in vertebrate retinal development and/or function. Immunohistochemical staining against *JAK1* was detected in two areas of the adult mouse brain, the olfactory bulb and a group of cells in the hypothalamus. Together, these expression studies suggest a role for *JAK1*

kinase in the differentiation or function of a subset of CNS neurons.
Descriptors: Aging--Metabolism--ME; *Brain--Enzymology--EN; *Central Nervous System--Enzymology--EN; *Eye--Enzymology--EN; **Gene* Expression; *Protein-Tyrosine Kinase--Biosynthesis--BI; *Protein-Tyrosine Kinase --Genetics--GE; *RNA, Messenger--Biosynthesis--BI; Amino Acid Sequence; Base Sequence; Brain--Growth and Development--GD; Cloning, Molecular; DNA; Eye--Growth and Development--GD; *Gene* Library; Mice; Molecular Sequence Data; Oligodeoxyribonucleotides; Polymerase Chain Reaction--Methods--MT; Protein-Tyrosine Kinase--Analysis--AN; Recombinant Fusion Proteins --Analysis--AN; Recombinant Fusion Proteins--Biosynthesis...
?ds

Set	Items	Description
S1	759	(JAK? (W) KINASE?)
S2	261	S1 AND (DNA OR VECTOR?)
S3	112	S2 AND (TYROSINE (W) PHOSPHORYLATION)
S4	65	S3 AND (CYTOKINE?)
S5	34	RD (unique items)
S6	14	S5 NOT PY>1996
S7	0	(JAK? (W) KINASE (W) PEPTIDE?)
S8	46	S1 AND REVIEW?
S9	37	RD (unique items)
S10	9	S9 AND (CYTOKINE AND (TYROSINE (W) PHOSPHORYLATION))
S11	310	S1 AND (CDNA OR GENE)
S12	167	RD (unique items)
S13	112	S12 AND (JAK1 OR JAK2 OR JAK3 OR TYK2)
S14	3	S13 NOT PY>1993

```
?s s12 and (Jak3)
             167  S12
             855  JAK3
     S15      29  S12 AND (JAK3)
?s s15 not py>1996
              29  S15
         5172566  PY>1996
     S16      19  S15 NOT PY>1996
?t s16/3,k/all
```

16/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09022989 98039350
Physiologic roles of interleukin-2, interleukin-4, and interleukin-7.
Murray R
DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, CA 94304, USA.
Current opinion in hematology (UNITED STATES) May 1996, 3 (3) p230-4, ISSN 1065-6251 Journal Code: CN0
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

The use of *gene* targeting techniques has led to new insights into the physiologic function of lymphoid growth factors, their receptors, and associated signal transduction molecules in the formation...

...tissues. Interleukin-2, interleukin-4, and interleukin-7 all utilize the common gamma (gamma c) receptor component at the cell surface of lymphocytes and the *Jak3* *kinase* molecule to transduce signals inside the cell. Both gamma c- and *Jak3* *kinase*-deficient animals display a phenotype similar to interleukin-7-deficient animals in terms of lymphoid development. Collectively, these genetic experiments clearly define different in vivo...

16/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09013460 97047914

Expression, characterization, and genomic structure of carp *JAK1* *kinase* *gene*.

Chang MS; Chang GD; Leu JH; Huang FL; Chou CK; Huang CJ; Lo TB
Department of Zoology, National Taiwan University, Taipei.

DNA and cell biology (UNITED STATES) Oct 1996, 15 (10) p827-44, ISSN 1044-5498 Journal Code: AF9
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Expression, characterization, and genomic structure of carp *JAK1* *kinase* *gene*.

A 3.7-kb *cDNA* encodes the carp *JAK1* *kinase* of 1,156 amino acid residues. The overall amino acid sequence identity between carp JAK1 and murine JAK1, JAK2, *JAK3*, and human TYK2 is 57%, 35.5%, 31.3%, and 42.4%, respectively. In addition, carp JAK1 shows higher sequence homology to mammalian JAK1 in...

... and c-JH2 associate with each other and c-JH2 can be tyrosine-phosphorylated by c-JAK1 and by c-JH(1 + 2). The JAK1 *gene* was also isolated from a carp genomic library and characterized. This *gene* is divided into 24 exons spanning at least 31 kb of genomic DNA. Exon 1 contains the 5'-untranslated region and exon 2 contains the...

...transcription factors including NF-IL6, HNF-5, AP1, GHF-5, and E2A. When this DNA fragment was placed upstream of the chloramphenicol acetyltransferase (CAT) reporter *gene* and transfected into a carp CF cell line, it could drive the synthesis of CAT enzyme 16 times more efficiently than the promoterless pCAT-Basic...

... region did not have detectable promoter activity. This suggests that this region of DNA may play an important role in the expression of carp JAK1 *gene*.

; Amino Acid Sequence; Base Sequence; Chloramphenicol O-Acetyltransferase ; DNA, Complementary; Exons; *Gene* Expression; *Gene* Library; Introns; Mammals; Mice; Molecular Sequence Data; Polymerase Chain Reaction; Protein-Tyrosine Kinase--Biosynthesis--BI; Proteins--Chemistry--CH; Recombinant Fusion Proteins--Biosynthesis--BI; Recombinant Fusion...

16/3,K/3 (Item 3 from file: 155)

09008440 96408718

Interactions among Janus kinases and the prolactin (PRL) receptor in the regulation of a PRL response element.

Gao J; Hughes JP; Auperin B; Buteau H; Edery M; Zhuang H; Wojchowski DM; Horseman ND
Department of Molecular and Cellular Physiology, University of Cincinnati, Ohio 45267-0576, USA.

Molecular endocrinology (UNITED STATES) Jul 1996, 10 (7) p847-56, ISSN 0888-8809 Journal Code: NGZ
Contract/Grant No.: DK-44895, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

PRL regulates milk *gene* expression, at least in part, by activating *JAK2* *kinase* and STAT5 (signal transducer and activator of transcription 5), initially termed mammary gland factor (MGF). These experiments were initiated to gain a better understanding of...

... signaling. Binding of PRL to the recombinant pigeon PRL-R-activated transcription driven by a 2.8 kbp 5'-fragment of the rat beta-casein *gene*

. PRL enhanced the expression of chimeric reporters containing the beta-casein PRL response element (PRE), but not the c-fos sis-inducible element, when the...

... entire extracellular ligand-binding domain, was only slightly more effective than a truncation mutant with a single extracellular domain. Transfection with either JAK1, JAK2, or *JAK3* increased basal transcription through both the PRE and sis-inducible element. Coexpression of JAK2 with PRL-R resulted in amplification of the induction of the...

... and 3 did not amplify the PRL effect. Overexpression of JAK2 mutants blocked PRE activation by PRL. Mutant JAK2 also interfered with PRE activation by *JAK3* but did not affect JAK1's stimulatory effect.

16/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08981001 97254528

***Jak3* expression in glomerular epithelia of IgA nephropathy (IgA-N) patients.**

Takahashi T; Shirasawa T; Miyake K; Yahagi Y; Matsumura O; Abe A; Natori Y; Yamabe H; Utsunomiya Y; Maruyama N; Mitarai T; Sakai O
Department of Molecular Pathology, Tokyo Metropolitan Institute of Gerontology, Itabashi-ku, Japan.

Clinical and experimental immunology (ENGLAND) Jun 1996, 104 (3) p517-24, ISSN 0009-9104 Journal Code: DD7
Languages: ENGLISH
Document type: JOURNAL ARTICLE

***Jak3* expression in glomerular epithelia of IgA nephropathy (IgA-N) patients.**

Jak3 is a member of the Janus kinase family which plays an important role in cytokine signal transduction. *Jak3* associates the gamma(c) chain of receptors for IL-2, IL-4, IL-7, IL-9 and IL-15, and is essential for the signal transduction of these cytokines. We have isolated *Jak3* *kinase* from renal mesangial cells and demonstrated the constitutive expression of *Jak3* in glomeruli in vivo. To investigate the physiological and pathological role of *Jak3* in glomeruli, we prepared anti-*Jak3* antibody and analysed the localization of *Jak3* in glomeruli of renal biopsy samples from various nephritis patients and normal subjects. Among 61 nephritis patients and four normal subjects investigated in the present study, *Jak3* was selectively localized to glomerular epithelia of IgA-N patients (14/34 cases) and focal glomerulosclerosis patients (1/5 cases), but not detected in minimal changes (n = 6), membranous glomerulonephropathy (n = 7), crescentic glomerulonephritis (n = 4), lupus nephritis patients (n = 5), and normal subjects (n = 4). The intense immunoreactivity for *Jak3* is significantly associated with the decrease in creatinine clearance (81.5 +/- 10.4 ml/min versus 104.3 +/- 29.6 ml/min; P < 0.05...

... 0.75 +/- 0.23 mg/dl; P < 0.01, Student's t-test) in IgA-N patients. Furthermore, gamma(c) chain was concomitantly expressed with *Jak3* in glomerular epithelia in vivo and in vitro, suggesting that signal transduction via gamma(c)-*Jak3* cascade may be involved in the pathogenesis of glomerular injury of IgA-N. Taken together with the recent findings that IL-4-secreting T lymphocytes...

; Biopsy; Blotting, Northern; Cells, Cultured; Creatinine--Blood--BL; Creatinine--Metabolism--ME; Electrophoresis, Polyacrylamide Gel; Epithelium--Metabolism--ME; *Gene* Expression Regulation; Glomerulonephritis--Metabolism--ME; Glomerulonephritis, IGA--Genetics--GE; Glomerulonephritis, Membranous--Metabolism--ME; Glomerulosclerosis, Focal--Metabolism--ME; Immunohistochemistry; Kidney--Pathology--PA; Lupus Nephritis--Metabolism--ME...

16/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08771826 96282847
Convergence of signaling transduced by prolactin (PRL)/cytokine chimeric receptors on PRL-responsive *gene* transcription.
Ferrag F; Chiarenza A; Goffin V; Kelly PA
INSERM U. 344, Faculte de Medecine Necker, Paris, France.
Molecular endocrinology (UNITED STATES) Apr 1996, 10 (4) p451-60, ISSN 0888-8809 Journal Code: NGZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Convergence of signaling transduced by prolactin (PRL)/cytokine chimeric receptors on PRL-responsive *gene* transcription.
... by receptors for the interleukin (IL)-3, IL-5, and granulocyte macrophage-colony stimulating factor, which share the common beta c-subunit. Otherwise, Jak1 and *Jak3* are involved in IL-2 signaling through heterodimerization of the IL-2 receptor-beta (IL-2R beta) and gamma c-chains. Stat5, a member of...

... 2R beta function as a complete signal transducer. Our data strengthen previous observations that Stat5 activation is not dependent on the activation of a specific *Jak* *kinase* and also suggest that neither *Jak3* nor gamma c have a specific role in this process.

16/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08650925 96228302
Tyrosyl phosphorylation and DNA binding activity of signal transducers and activators of transcription (STAT) proteins in hematopoietic cell lines transformed by Bcr/Abl.
Carlesso N; Frank DA; Griffin JD
Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.
Journal of experimental medicine (UNITED STATES) Mar 1 1996, 183 (3) p811-20, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: RO1 DK43904, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

... Janus family kinases (JAKs) and subsequent tyrosyl phosphorylation of STAT proteins (signal transducers and activators of transcription). This pathway directly links growth factor receptors to *gene* transcription. We analyzed JAK activation, STAT protein phosphorylation, and the formation of specific DNA-binding complexes containing STAT proteins, in a series of leukemia cell...

... DNA-STAT complexes in 32Dp210Bcr/Abl cells were similar, but not identical, to those formed after IL-3 stimulation. It is interesting to note that *JAK* *kinases* (JAK1, JAK2, *JAK3* , and Tyk2) were not consistently activated in Bcr/Abl-positive cells. These data suggest that STATs can be activated directly by Bcr/Abl, possibly bypassing...

16/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08582651 95391962
***JAK3* protein tyrosine kinase mediates interleukin-7-induced activation**

of phosphatidylinositol-3' kinase.
Sharfe N; Dadi HK; Roifman CM
Division of Immunology and Allergy, Hospital for Sick Children, University of Toronto, Ontario, Canada.
Blood (UNITED STATES) Sep 15 1995, 86 (6) p2077-85, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE

***JAK3* protein tyrosine kinase mediates interleukin-7-induced activation of phosphatidylinositol-3' kinase.**
... tyrosine kinase domain, mediates tyrosine phosphorylation in T cells. We have identified IL-7-induced activation of three cyoplasmic tyrosine kinases in T cells, Jak1, *Jak3*, and the src-like kinase p56lck. Many members of the cytokine receptor superfamily activate the Jak protein tyrosine kinase family, with resultant phosphorylation of the Stat transcriptional activator factors. We describe here a novel function of the *Jak* *kinases*, because *Jak* *kinase* activity is not only required for Stat activation but also for P13 kinase response to IL-7 in human T cells. We show that IL...

... of the P13 kinase p85 subunit, is essential to the IL-7 proliferative signal and also occurs in the absence of src family kinase activity. *Jak3* is found associated with the p85 subunit of P13 kinase in an IL-7-responsive manner in T cells and appears to regulate IL-7-induced P13 kinase activation by mediating tyrosine phosphorylation of the p85 subunit. Specific inhibition of IL-7-induced *Jak* *kinase* activity ablates p85 tyrosine phosphorylation, subsequent P13 kinase activation, and, ultimately, proliferation. The ability to regulate P13 kinase activity indicates a more generalized role for the Jak family than activation of *gene* transcription via the Stat family in cytokine receptor signal transduction.

16/3,K/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08582351 95386713
Constitutive activation of different Jak tyrosine kinases in human T cell leukemia virus type 1 (HTLV-1) tax protein or virus-transformed cells.
Xu X; Kang SH; Heidenreich O; Okerholm M; O'Shea JJ; Nerenberg MI
Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, California 92037, USA.
Journal of clinical investigation (UNITED STATES) Sep 1995, 96 (3) p1548-55, ISSN 0021-9738 Journal Code: HS7
Contract/Grant No.: NS-12428, NS, NINDS; CA-5023, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

...1 transformed human lymphoid lines, but not in thymocytes from Thy-tax transgenic mice. Phosphotyrosine immunoprecipitation followed by Western blot analysis with a set of *Jak* *kinase* specific antibodies, identified p130 as Jak2 in the tax transformed mouse fibroblastic cell line and *Jak3* in HTLV-1 transformed human T cell lines. Phosphorylation of Jak2 in tax transformed cells resulted from high expression of IL-6. Tyrosine phosphorylation of...

... the B line, which was associated with induction of cell proliferation. Both phosphorylation and proliferation were inhibited by IL-6 neutralizing antibodies. Constitutive phosphorylation of *Jak* *kinases* may facilitate tumor growth in both HTLV-1 infected human T cells and the transgenic mouse model.
Descriptors: Cell Transformation, Viral; **Gene* Products, tax --Biosynthesis--BI; *HTLV-I--Genetics--GE; *Protein-Tyrosine Kinase --Metabolism--ME; Base Sequence; Cell Division--Drug Effects--DE; Cell Line

; DNA Primers; Enzyme Activation; *Gene* Expression; HTLV-I--Metabolism--ME ; Interleukin-6--Biosynthesis--BI; Interleukin-6--Pharmacology--PD; Kinetics; Mice; Mice, Transgenic; Molecular Sequence Data; NF-kappa B --Metabolism--ME...
Chemical Name: Janus kinase 2; (Janus kinase 3; (Protein-Tyrosine Kinase; (DNA Primers; (*Gene* Products, tax; (Interleukin-6; (NF-kappa B; (Oligonucleotide Probes; (Receptors, Interleukin; (Receptors, Interleukin-6

16/3,K/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08388855 95169058
Structural domains of interleukin-2 receptor beta critical for signal transduction: kinase association and nuclear complex-formation.
Howard OM; Kirken RA; Garcia GG; Hackett RH; Farrar WL
Biological Carcinogenesis and Development Program, NCI-Frederick Cancer Research and Development Center, MD 21702.
Biochemical journal (ENGLAND) Feb 15 1995, 306 (Pt 1) p217-24, ISSN 0264-6021 Journal Code: 9YO
Languages: ENGLISH
Document type: JOURNAL ARTICLE

... the p116 kinase in the receptor complex correlates with IL-2-induced proliferation. An IL-2-inducible p116 kinase has recently been characterized as a *Jak* *kinase* family member and named *Jak3*. Nuclear complexes were formed with the GRR oligomer only when the IL-2R beta mutant supported proliferation. This led us to conclude that Box1-Box2 and PQPLXP motifs associate with *Jak3* and that this association is an essential element in the IL-2 signal-transduction pathway culminating in the formation of a nuclear complex.
; Amino Acid Sequence; Base Sequence; Cell Division; Cell Line; *Gene* Deletion; Lymphocytes; Mice; Molecular Sequence Data; Mutagenesis; Plasmids; Receptors, Interleukin-2--Genetics--GE; Structure-Activity Relationship; Transfection; Tyrosine--Analogs and Derivatives--AA; Tyrosine--Analysis--AN...

16/3,K/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08297650 95276241
Tyrosine phosphorylation and activation of JAK family tyrosine kinases by interleukin-9 in MO7E cells.
Yin T; Yang L; Yang YC
Walther Oncology Center, Indiana University Medical Center, Indianapolis 46202, USA.
Blood (UNITED STATES) Jun 1 1995, 85 (11) p3101-6, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: R01HL48819, HL, NHLBI; R01DK43105, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

... have not been identified. In this report we show that IL-9 induces tyrosine phosphorylation and activation of the JAK family tyrosine kinases including JAK1, *JAK3* , and Tyk2. The kinetic studies indicate that tyrosine phosphorylation and activation of *JAK* *kinases* induced by IL-9 occurred within 1 minute, peaked by 5 to 10 minutes, and persisted at least for 45 minutes. Furthermore, we show that...

... 9 specifically interact with a DNA element termed gamma activated site. These results suggest that actions of IL-9 may, in part, be mediated through *JAK* *kinase*-Stat signaling cascades.

; Base Sequence; DNA-Binding Proteins--Metabolism--ME; Enzyme Activation --Drug Effects--DE; *Gene* Expression Regulation, Leukemic--Drug Effects --DE; Leukemia, Megakaryocytic, Acute--Pathology--PA; Molecular Sequence Data; Phosphorylation--Drug Effects--DE; Regulatory Sequences, Nucleic Acid ; Signal Transduction--Drug...

16/3,K/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08164222 94309920
***JAK3*: a novel *JAK* *kinase* associated with terminal differentiation of hematopoietic cells.**
Rane SG; Reddy EP
Department of Biochemistry, Temple University School of Medicine, Philadelphia, PA 19140.
Oncogene (ENGLAND) Aug 1994, 9 (8) p2415-23, ISSN 0950-9232 Journal Code: ONC
Contract/Grant No.: CA 52009, CA, NCI; CA 12227, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

***JAK3*: a novel *JAK* *kinase* associated with terminal differentiation of hematopoietic cells.**
... play a pivotal role in the signal transduction process mediated by cytokines. These kinases appear to transduce signals via their substrates which modulate programs of *gene* expression specific to the respective signals. It is becoming increasingly evident that certain cytokines such as Granulocyte Colony Stimulating Factor (GCSF) can transmit signals for both cellular proliferation and differentiation. It is at present unclear whether both of these signals are transmitted by the same *JAK* *kinase* or whether an entire family of such kinases are involved in this process. To determine if additional members of *JAK* *kinase* family exist, we designed a polymerase chain reaction based strategy which resulted in the identification of a new member of the *JAK* *kinase* family. This new kinase, which we have named *JAK3* is encoded by a 4.3 kb mRNA transcript. Nucleotide sequence analysis of a full length *cDNA* derived from this mRNA revealed that it encodes an open reading frame of 3897 bp. The protein encoded by this mRNA contains the double catalytic domain characteristic of the JAK family kinases. The most striking difference between *JAK3* and the other *JAK* *kinases* is the presence of two stretches of additional amino acid sequence of 147 and 28 residues which span between amino acid positions 322 to 469 and 632 to 660 respectively. Expression studies indicate that *JAK3* is expressed at very low levels in immature hematopoietic cells, but its expression is dramatically up-regulated during terminal differentiation of these cells. These results suggest that *JAK3* plays an important role in the differentiation of hematopoietic cells.
; Amino Acid Sequence; Base Sequence; Cell Differentiation; Cell Line; Cloning, Molecular; DNA, Complementary--Chemistry--CH; DNA, Complementary --Isolation and Purification--IP; *Gene* Expression Regulation; Granulocyte Colony-Stimulating Factor--Pharmacology--PD; Mice; Molecular Sequence Data; Polymerase Chain Reaction; Protein-Tyrosine Kinase--Chemistry--CH; Protein-Tyrosine Kinase--Physiology--PH

16/3,K/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07894320 94192816
Molecular cloning of rat *JAK3*, a novel member of the JAK family of protein tyrosine kinases.
Takahashi T; Shirasawa T
Department of Molecular Pathology, Tokyo Metropolitan Institute of Gerontology, Japan.

FEBS letters (NETHERLANDS) Apr 4 1994, 342 (2) p124-8, ISSN 0014-5793
Journal Code: EUH
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Molecular cloning of rat *JAK3*, a novel member of the JAK family of protein tyrosine kinases.

We have cloned and sequenced a *cDNA* (*JAK3*) encoding a novel member of the JAK family of protein tyrosine kinases. *JAK3* was identified by RT-PCR of rat mesangial cells using degenerate oligonucleotide primers, and a full-length clone was isolated from a rat spleen *cDNA* library. The primary structure of *JAK3* showed *cDNA* with an open reading frame of 1,100 amino acids which comprises the PTK catalytic domain and a second kinase-related domain characteristic for *JAK* *kinase*. *JAK3* was phylogenetically shown to be most closely related to JAK2 among the previously known JAK family members, JAK1, JAK2 and Tyk2. Southern analysis revealed that *JAK3* is a single copy *gene* and well conserved in the vertebral genome. Northern analysis indicated that the 4.0 kb mRNA was transcribed in a variety of tissues including spleen...

Gene Symbol: *JAK3*

16/3,K/13 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06718315 EMBASE No: 1996259169

Immunodeficiencies caused by genetic defects in protein kinases

Notarangelo L.D.
L.D. Notarangelo, Department of Pediatrics, University of Brescia, Spedali Civili, 25123 Brescia Italy

Current Opinion in Immunology (CURR. OPIN. IMMUNOL.) (United Kingdom) 1996, 8/4 (448-453)
CODEN: COPIE ISSN: 0952-7915
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The recognition that defects of ZAP-70 and, more recently, of *JAK3* *kinase* in humans result in severe combined immunodeficiency, and the demonstration that targeting of these and other protein-kinase genes in mice also leads to immunodeficiency...

MEDICAL DESCRIPTORS:
gene targeting; human; lymphocyte differentiation; lymphocyte proliferation; nonhuman; phenotype; review; t lymphocyte activation

16/3,K/14 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06547832 EMBASE No: 1996208177

CD40-mediated regulation of interleukin-4 signaling pathways in B lymphocytes

Siepmann K.; Wohlleben G.; Gray D.
Department of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road,London W12 0NN United Kingdom

European Journal of Immunology (EUR. J. IMMUNOL.) (Germany) 1996, 26/7 (1544-1552)
CODEN: EJIMA ISSN: 0014-2980
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...to CD40-prestimulated cells provokes intracellular signals distinct from those induced in resting B cells in response to IL-4. While resting B cells phosphorylate *Jak3* *kinase* shortly after IL-4 activation, cells pre-incubated with anti-CD40 exhibit active dephosphorylation of this

molecule and phosphorylation of proteins of around 45 kDa upon addition of IL-4. The common gamma chain, *Jak3* and Jak1 can all be immunoprecipitated in normal amounts with the IL-4R chain after CD40 prestimulation. We show that the observed dephosphorylation of *Jak3* may be due to a stable association with the src-homology protein tyrosine phosphatase SH-PTP2. In contrast, the enzyme appears to be inactive and...
MEDICAL DESCRIPTORS:
animal cell; article; b lymphocyte activation; cell surface; controlled study; dephosphorylation; female; *gene* mutation; immunoprecipitation; mouse; nonhuman; priority journal; protein phosphorylation; receptor affinity

16/3,K/15 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06009389 EMBASE No: 1995038044
Tyrosine phosphorylation of p95(Vav) in myeloid cells is regulated by GM-CSF, IL-3 and Steel factor and is constitutively increased by p210(BCR-ABL)
Matsuguchi T.; Inhorn R.C.; Carlesso N.; Xu G.; Druker B.; Griffin J.D.
Division of Hematologic Malignancies, Dana-Farber Cancer Institute, 44 Binney Street,Boston, MA 02115 United States
EMBO Journal (EMBO J.) (United Kingdom) 1995, 14/2 (257-265)
CODEN: EMJOD ISSN: 0261-4189
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...to induce tyrosine phosphorylation of p95(Vav) are also known to activate JAK family tyrosine kinases, we looked for an interaction of p95(Vav) with *JAK* *kinases*, p95(Vav) co-precipitated with JAK2 in MO7e cells stimulated with GM-CSF, but not in unstimulated cells. Also, JAK2 was found to be constitutively...

...SH2) precipitated JAK2, suggesting that this interaction is mediated by the SH2 domain of p95(Vav). GST-VaV-SH2, but not GST, also precipitated JAK1, *JAK3* and Tyk2, suggesting that other JAK family kinases might interact with p95(Vav). These results suggest that tyrosine phosphorylation of p95(Vav) is potentially directly regulated by *JAK* *kinases*, and further suggest that Vav is broadly involved in signal transduction in myeloid cells initiated by many cytokines and the oncogene BCR/ABL.
MEDICAL DESCRIPTORS:
article; bone marrow cell; bone marrow culture; cell lysate; controlled study; enzyme activity; *gene* induction; hematopoietic cell; human; human cell; priority journal; protein family; protein phosphorylation; signal transduction

16/3,K/16 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

05708576 EMBASE No: 1994107734
Molecular cloning of rat *JAK3*, a novel member of the JAK family of protein tyrosine kinases
Takahashi B.T.; Shirasawa T.
Department of Molecular Pathology, Tokyo Metropolitan Inst. Gerontology, 35-2 Sakae-cho,Itabashi-ku, Tokyo 173 Japan
FEBS Letters (FEBS LETT.) (Netherlands) 1994, 342/2 (124-128)
CODEN: FEBLA ISSN: 0014-5793
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Molecular cloning of rat *JAK3*, a novel member of the JAK family of protein tyrosine kinases